



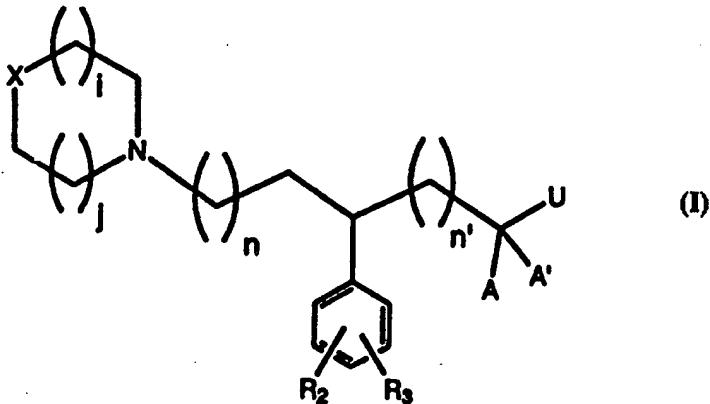
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(54) Title: PIPERIDINE DERIVATIVES AS NEUROKININ ANTAGONISTS

(57) Abstract

The invention relates to compounds of formula (I), wherein X, i, j, n, n', A, A', R₂, R₃, and U are as described herein. The compounds of the invention are NK₁ or NK₂ or NK₃ receptor antagonists and as such are useful in the treatment of diseases such as asthma.



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PIPERIDINE DERIVATIVES AS NEUROKININ ANTAGONISTS

5 BACKGROUND OF THE INVENTION

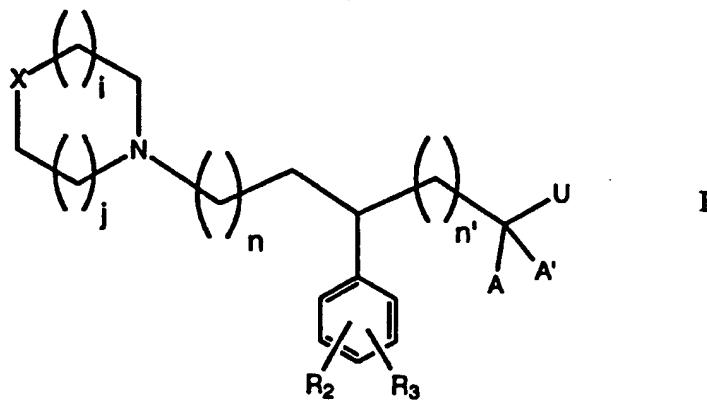
The present invention relates to a genus of compounds useful as antagonists of neurokinin receptors. In particular, these can be neurokinin-1 receptor (NK₁) antagonists, neurokinin-2 receptor (NK₂) antagonists, and neurokinin-3 receptor (NK₃) antagonists.

10 Neurokinin receptors are found in the nervous system and the circulatory system and peripheral tissues of mammals, and therefore are involved in a variety of biological processes. Neurokinin receptor antagonists are consequently expected to be useful in the treatment or prevention of various mammalian disease states, for example asthma, 15 cough, bronchospasm, inflammatory diseases such as arthritis, migraine, nociception, and various gastrointestinal disorders such as Crohn's disease.

In particular, NK₁ receptors have been reported to be involved in microvascular leakage and mucus secretion, and NK₂ receptors have 20 been associated with smooth muscle contraction, making NK₁ and NK₂ receptor antagonists especially useful in the treatment and prevention of asthma.

Summary of the Invention

25 The invention relates to compounds of the formula



- 2 -

wherein each i and j is independently selected from the group consisting of 1 and 2;

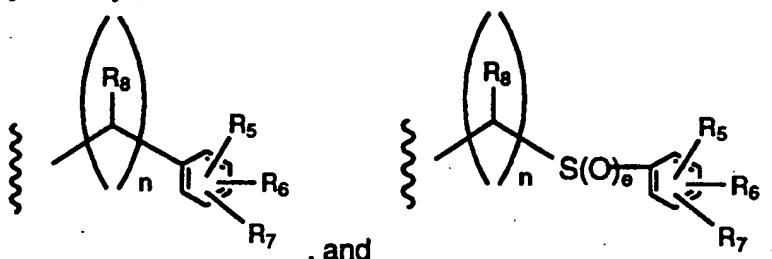
each n is independently selected from the group consisting of 0, 1, 2 and 3; and each n' is independently selected from the group consisting of 1, 2 and 3;

5 wherein A and A' are H, or A and A' taken together are =O, =S; or =N-R₄;

X is selected from the group consisting O, CO, C(R, R₁), C=C(R₁, R₈), NR₁, and S(O)_e wherein e is 0, 1, or 2;

10 R is selected from the group consisting of H, OR₈, CON(R₈)₂, CN, S(O)_eR₈, SO_eN(R₈)₂, CO₂R₈, and NR₄COR₈;

R₁ is selected from the group consisting of H, (C₁-C₆)-alkyl (C₃-C₈)-cyclo-alkyl,



15 R₂, R₃, R₅, R₆ and R₇ are independently selected from the group consisting of H, halogen, (C₁-C₆)-alkyl, CF₃, C₂F₅, OR₈, COR₈, CO₂R₈, CON(R₈, R₈), N(R₈, R₈), N(R₈)COR₈, S(O)_eR₈, OC(O)R₄, OC(O)N(R₈, R₄), NR₈CO₂R₄, NR₈(CO)N(R₈, R₈), R₁₅-phenyl, R₁₅-benzyl, NO₂, NR₈SO₂R₄, -S(O)₂N(R₈)₂ or when R₂ and R₃ or any two of R₅, R₆ and

20 R₇ are on adjacent carbons they may form a -O-CH₂-O- group;

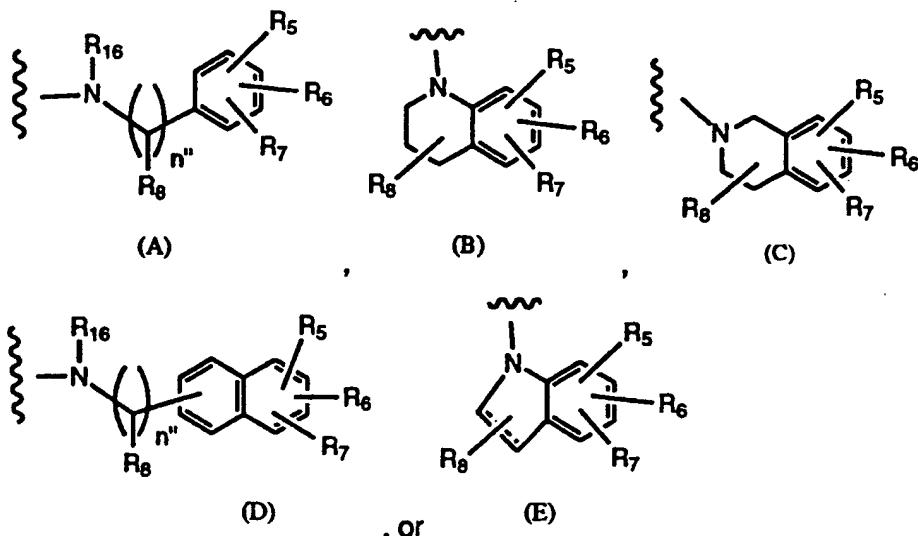
each R₄ is independently selected from the group consisting of alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

each R₈ is independently selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

25 each R₁₅ is independently H, halogen, lower alkyl, lower alkoxy; and

U is

- 3 -



n " is independently selected from the group consisting of 0, 1, 2 and 3;

5 the dashed line is an optional carbon-carbon bond;
 R_{16} is H, (C_1 - C_6)-alkyl, - $S(O)_2R_4$, COR_8 , CO_2R_4 , $CON(R_8)_2$, R_{15} .phenyl or R_{15} .benzyl.
Substituted means substituted with a substituent selected from the group consisting of H, (C_1 - C_6) alkyl, OCF_3 , CF_3 , and C_2F_5 .

10 Also preferred are compounds of formula I, wherein i is 1 and j is 1.
Also preferred are compounds of formula I, wherein n is 1, n'' is 0, 1, or 2, and n' is 1.
Also preferred are compounds of formula I, wherein n, n' and n'' are all 1.

15 Also preferred are compounds of formula I, wherein n and n' are both 1 and n'' is 0.
Also preferred are compounds of formula I, wherein n and n' are both 1 and n'' is 2.
Also preferred are compounds of formula I, wherein A and A' are both H.

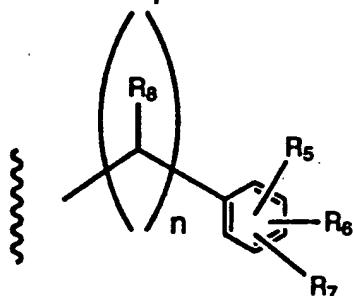
20 Also preferred are compounds of formula I, wherein A and A' taken together are =O.
Also preferred are compounds of formula I, wherein X is $C(R, R_1)$.
Also preferred are compounds of formula I, wherein R is OR_8 ,

25 $CON(R_8)_2$, CN , or NR_8COR_8 .

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Also preferred are compounds of formula I, wherein X is NR₁.

Also preferred are compounds of formula I, wherein R₁ is



Also preferred are compounds of formula I, where n is 0 or 1 and

5 R₈ is H.

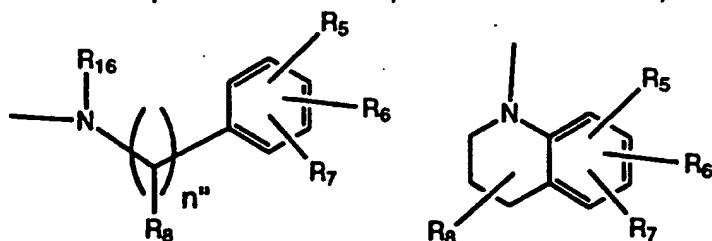
Also preferred are compounds of formula I, wherein R₂, R₃, R₅, R₆ and R₇ are H, halogen, C₁-C₆ alkyl, CF₃, OR₈, COR₈, CO₂R₈, CONR₈R₈, or NR₈R₈

10 Also preferred are compounds of formula I, wherein R₁₆ is H or alkyl.

Also preferred are compounds of formula I, wherein each R₈ is H, C₁-C₆ alkyl, or R₁₅-phenyl

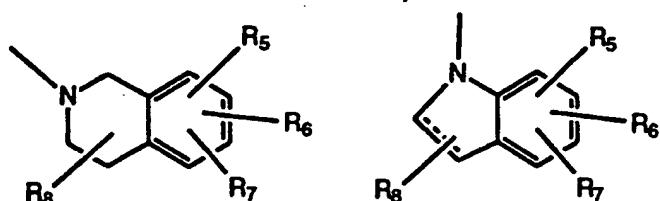
Also preferred are compounds of formula I, wherein R₈ is H or substituted alkyl.

15 Also preferred are compounds of formula I, wherein U is



(A)

(B)



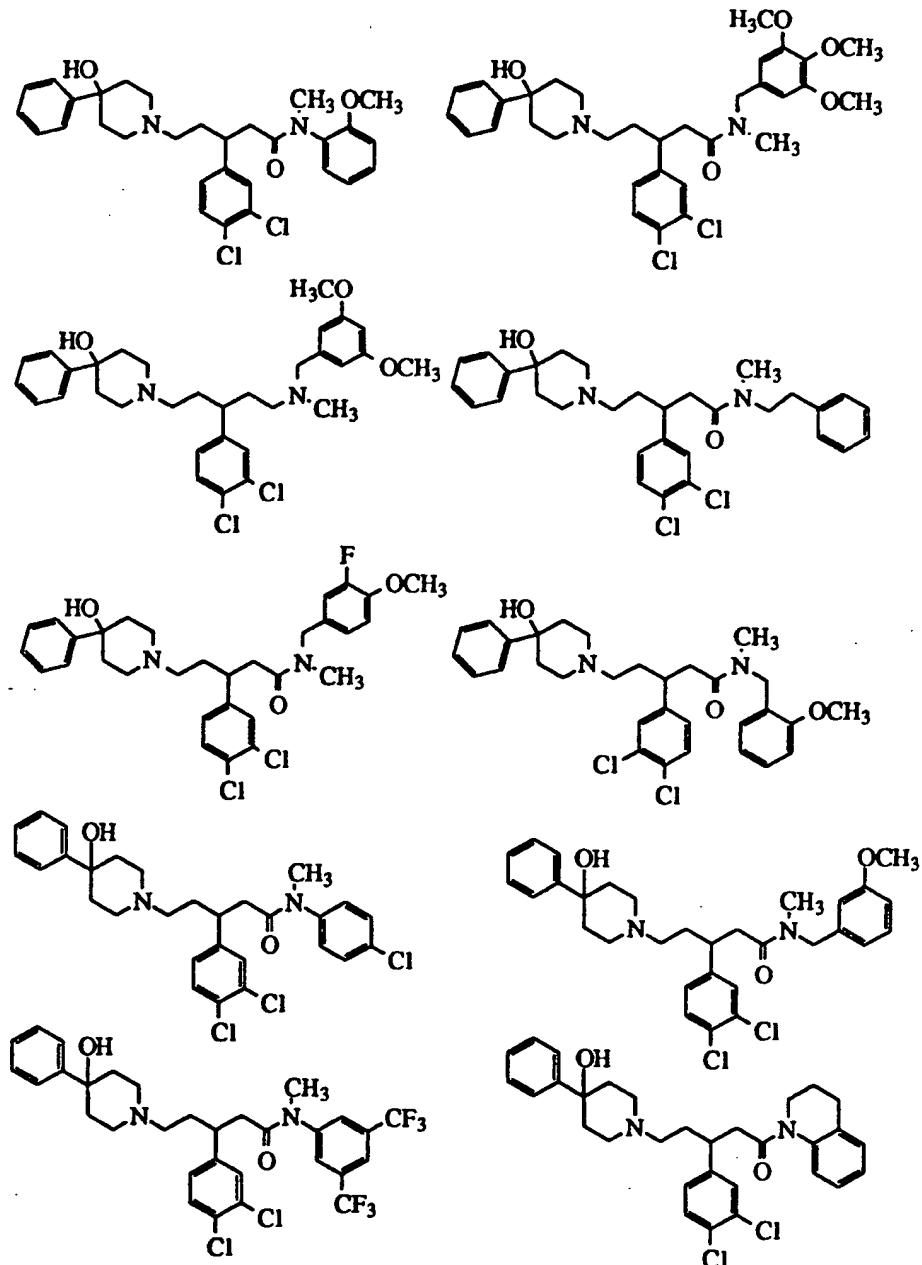
(C)

(D)

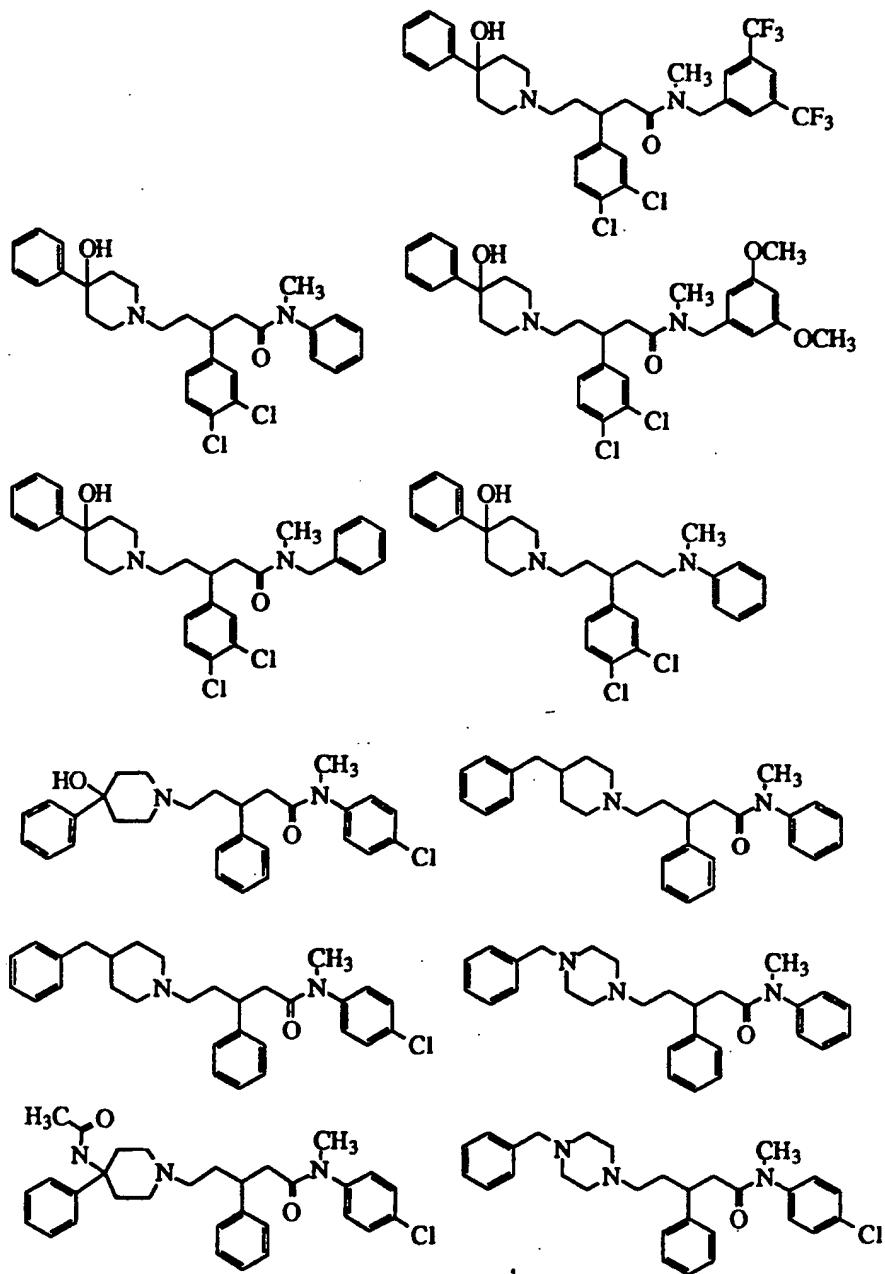
, or

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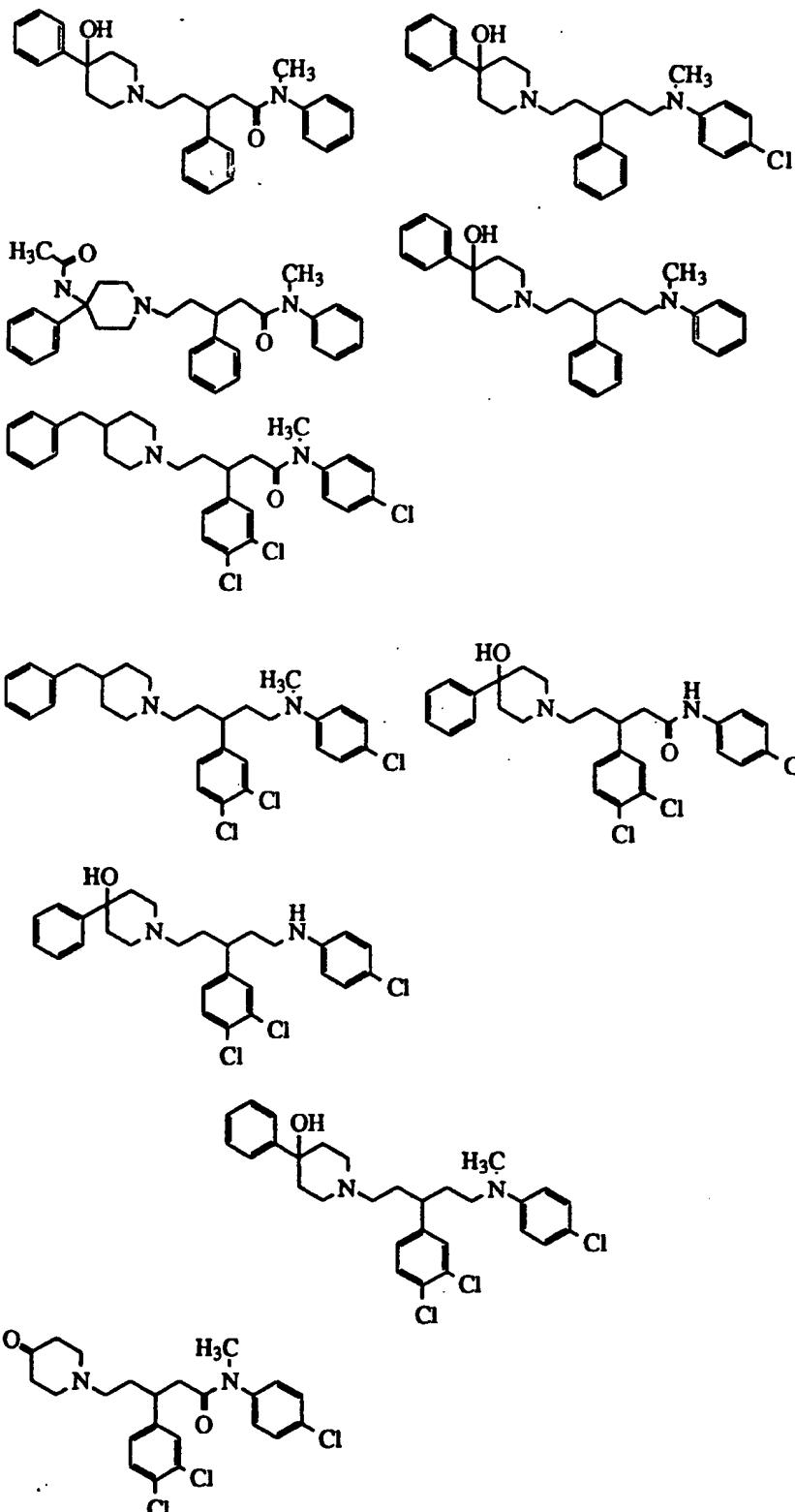
Exemplary compounds of the invention are the following, as well as pharmaceutically acceptable salts thereof:



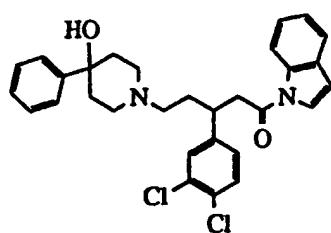
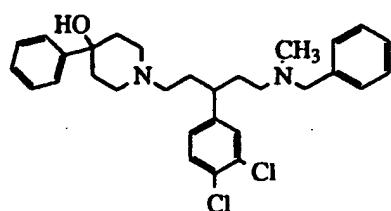
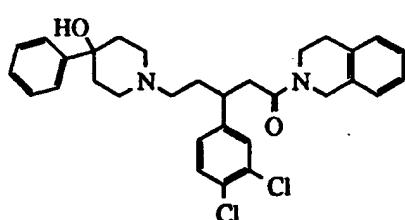
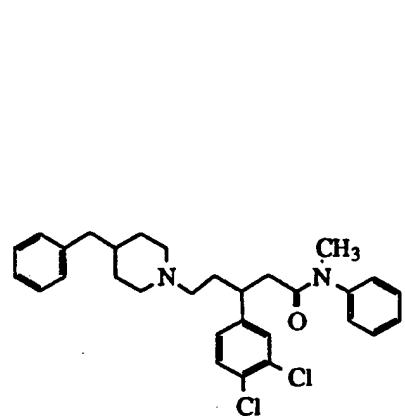
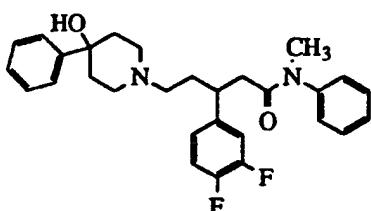
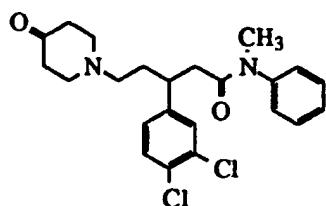
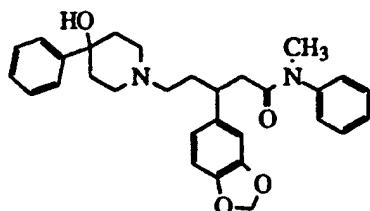
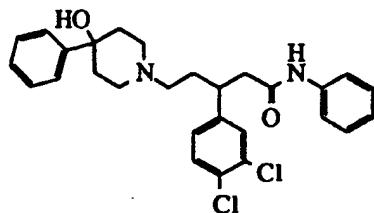
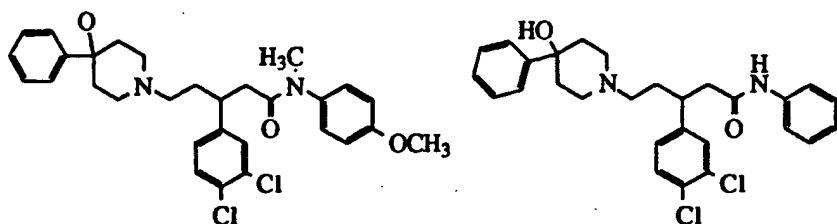
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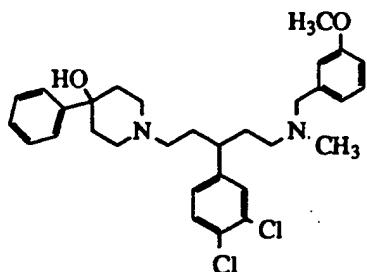
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The invention also relates to a composition comprising a neurokinin antagonistic effective amount of a compound according to
5 formula I and a pharmaceutically acceptable carrier material. The invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The invention also relates to a method for inducing neurokinin
10 antagonism which comprises administering a neurokinin antagonistic effective amount of a compound according to formula I to a mammal in need thereof. The invention also relates to a method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, osteoarthritis, and
15 rheumatoid arthritis; migraine; central nervous system disorders such as

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depression, psychosis, dementia, and Alzheimer's disease; Down's syndrome; neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto immune disorders; graft rejection; systemic lupus erythematosus; GI disorders such as Crohn's disease and ulcerative colitis; disorders of bladder function; circulatory disorders such as angina; Raynaud's disease; coughing and pain. In particular, the invention also relates to a method of treating asthma which comprises administering to a mammal in need of such treatment an anti-asthma effective amount of a compound of formula I for such purpose.

10

Detailed Description of the Invention

As used herein the term alkyl means a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C₁-C₆ alkyl" represents a straight or branched, saturated hydrocarbon having from 1 to 6 carbon atoms.

The term alkenyl means a straight or branched, saturated alkenyl having from 2 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C₂-C₆ alkenyl" represents a straight or branched alkenyl having from 1 to 6 carbon atoms.

Asymmetric centers exist in compounds of formula I of the invention. Accordingly, compounds of formula I include stereoisomers. All such isomeric forms and mixtures thereof are within the scope of the present invention. Unless otherwise indicated, the methods of preparation disclosed herein may result in product distributions which include all possible structural isomers, although it is understood that physiological response may vary according to stereochemical structure. The isomers may be separated by conventional means such as fractional crystallization, preparative plate or column chromatography on silica, alumina, or reversed phase supports or HPLC (high performance liquid chromatography).

Enantiomers may be separated, where appropriate, by derivatization or salt formation with an optically pure reagent, followed

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by separation by one of the aforementioned methods. Alternatively, enantiomers may be separated by chromatography on a chiral support.

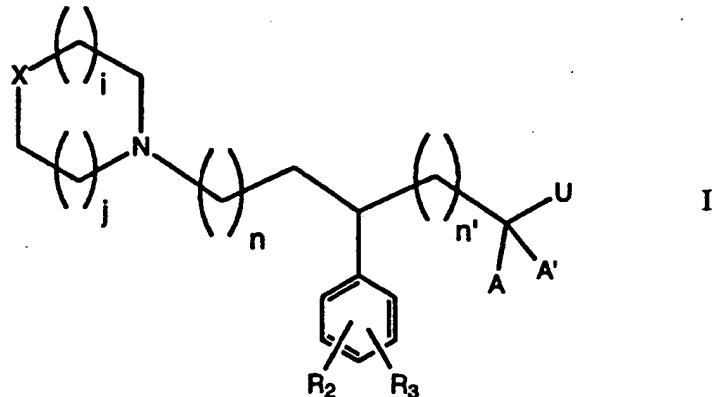
The compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g. the hemihydrate. In 5 general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unsolvated forms for the purposes of the invention.

Those compounds of formula I which contain a basic group such as $\text{-CH}_2\text{NH}_2$, form pharmaceutically acceptable salts. The preferred 10 pharmaceutically acceptable salts are nontoxic acid addition salts formed by adding to a suitable compound of the invention about a stoichiometric amount of a mineral acid, such as HCl, HBr, H_2SO_4 or H_3PO_4 or of an organic acid such as acetic, propionic, valeric, oleic, palmitic, stearic, lauric, benzoic, lactic, para-toluenesulfonic, methane 15 sulfonic, citric, maleic, fumaric, succinic and the like, respectively.

General Methods of Preparation

The compounds of this invention may be prepared by one 20 of the following general methods. Unless otherwise indicated, variables in the structural formulas below are as defined above.

The compounds of the present invention may be prepared from an appropriately substituted benzaldehyde as shown in Scheme 1 or from an appropriately substituted phenylacetic acid as shown in 25 Scheme 2.



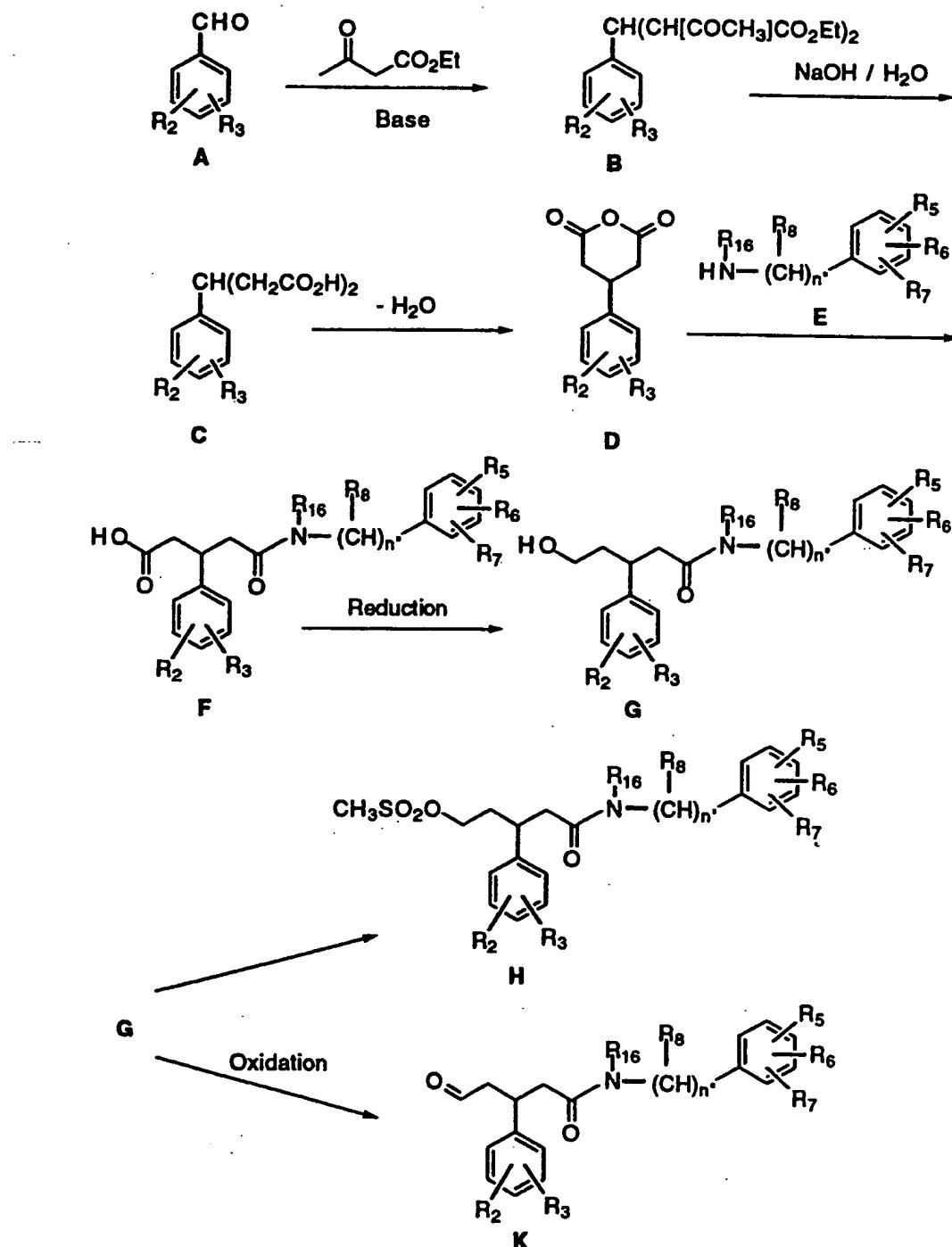
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Methods for preparing the compounds of the present invention are illustrated in the following Schemes and examples. The compounds of the present invention may be prepared from an appropriately substituted benzaldehyde as shown in Scheme 1 or from 5 an appropriately substituted phenylacetic acid as shown in Scheme 2.

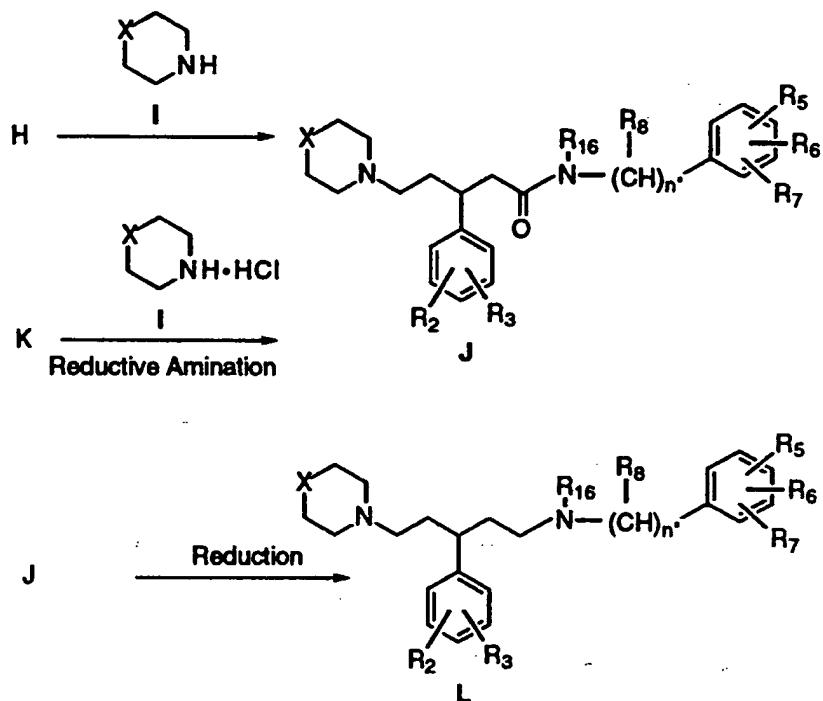
Thus, as shown in Scheme 1, a benzaldehyde A is condensed with ethylacetacetate in the presence of a base, for example an amine base such as piperidine, in a suitable solvent, for example an alcohol such as ethanol, as described in *J. Indian Chem. Soc.*, 1976, 53, 1122, to give a bisacetacetate B. Hydrolysis of B under strongly basic conditions using sodium hydroxide in an aqueous alcoholic solvent gives diacid C. Dehydration of C using an appropriate dehydrating agent, for example dicyclohexylcarbodiimide or acetyl chloride, then gives the substituted glutaric anhydride D. Treatment of 10 anhydride D with an aniline or an arylalkylamine E in a suitable solvent, for example a halogenated solvent such as dichloromethane, in the presence of a suitable base, for example triethylamine or N,N-dimethylaminopyridine (DMAP), gives acid F. Reduction of the carboxylic acid function of F using a suitable reduction procedure, for 15 example via the corresponding imidazolide or carbonic mixed anhydride and treatment with aqueous sodium borohydride, gives alcohol G. The alcohol G may then be converted to its corresponding halide or sulfonate H, for example by treatment with a sulfonyl halide in the presence of a base such as pyridine. Intermediate H may then be 20 condensed with heterocyclic amine I in a suitable solvent, for example N,N-dimethylformamide, in the presence of a base, for example potassium carbonate or N,N-diisopropylethylamine, if desired to give J. In an alternative embodiment alcohol G may be oxidized, for example by the Swern procedure as described in *Tetrahedron*, 1978, 34, 1651, to 25 give aldehyde K. Aldehyde K may then be condensed with heterocyclic amine I in a reductive amination reaction, for example using sodium cyanoborohydride in methanol in the presence of a dehydrating agent such as molecular sieves, similar to that described in *J. Amer. Chem. Soc.*, 1971, 93, 2897, to give J. The amide functionality of J may be 30

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reduced, for example using borane-dimethylsulfide in tetrahydrofuran, to give amine L.



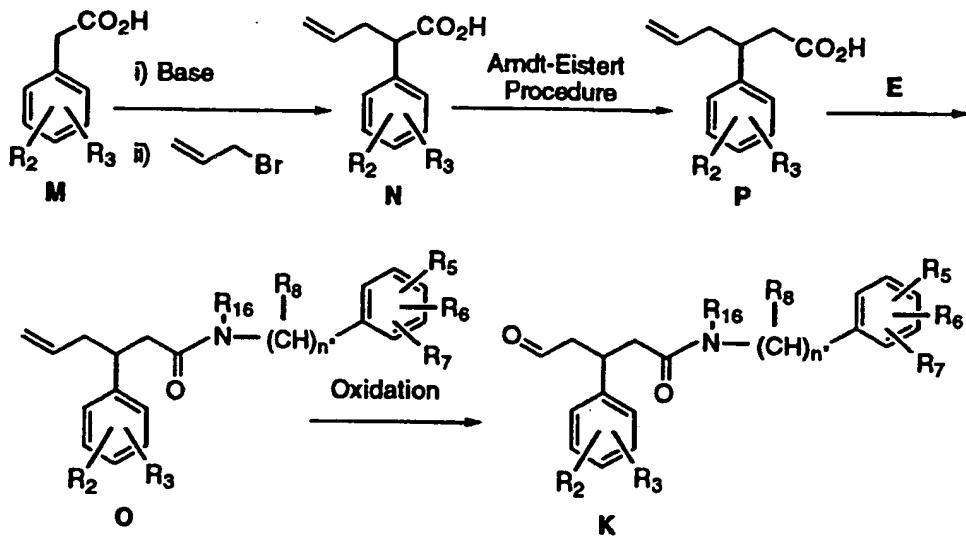
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In an alternative synthesis, Scheme 2, a phenylacetic acid

M may be converted to allyl acid N, for example as described in
 5 *Bioorganic Med. Chem. Letts.*, 1993, 3, 319. Acid N may be homologated to acid P according to the Arndt-Eistert procedure, for example as described in *Chem. Pharm. Bull.*, 1981, 29, 3249, and acid P may be condensed with an aniline or arylalkylamine E to give O (n = 1). Condensation of acid P may be accomplished via the corresponding
 10 acid chloride, prepared from P by treatment with oxalyl chloride and catalytic N,N-dimethylformamide, which may be used when E is an aniline or an arylalkylamine and is the preferred method when E represents an aniline. In an alternative procedure, when E is an arylalkylamine, condensation with P may be effected via the use of a
 15 carbodiimide, for example by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in dichloromethane. The allyl group of O can be oxidatively cleaved, for example upon treatment with ozone in methanol, to give aldehyde K. Aldehyde K may then be used in reductive amination reactions with heterocyclic amines I to give
 20 compound J as illustrated in Scheme 1.

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Scheme 2.

The invention disclosed herein is exemplified by the following examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention will be apparent to those skilled in the art.

Example 1

10 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl-1-piperidinpentamide

Step A Diethyl-3,4-dichlorobenzal-bis-acetoacetate

15 3,4-Dichlorobenzaldehyde (100 g) in 95% ethanol (120 mL) was treated with ethylacetoacetate (146 mL) and stirred until a homogenous solution was obtained. This solution was treated with piperidine (8 mL) and left to stand for 18 hours. The crude product was recrystallized from 95% ethanol to give the title compound (230 g).

20 Step B 3-(3,4-Dichlorophenyl)glutaric acid

Diethyl-3,4-dichlorobenzal-bis-acetoacetate (155 g) in ethanol 2 L was treated with 50% NaOH (2 L) and heated at reflux temperature for 4 hours. Water (1 L) was added to the reaction mixture and approx. 1.5 L of solvent removed by distillation. The remaining solution was poured

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onto ice (1 Kg) and sufficient HCl was added to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 X 1.5 L) and the combined extracts dried over MgSO₄, filtered and concentrated to give 100 g of the title compound.

5

Step C 3-(3,4-Dichlorophenyl)glutaric anhydride

3-(3,4-Dichlorophenyl)glutaric acid (100 g) was treated with acetyl chloride (300 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene and 10 concentrated under reduced pressure. The residue was slurried with diethyl ether (250 mL) and filtered to afford the title compound (86 g).

Step D 3,4-Dichloro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

15 3-(3,4-Dichlorophenyl)glutaric anhydride in CH₂Cl₂ (20 mL) at 0°C was treated sequentially with N-methylaniline (0.518 g), triethylamine (0.489 g) and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X20 mL) and water (20 mL).
20 The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (1.2 g).

Step E 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide

25 3,4-Dichloro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (0.98 g) in EtOAc (25 mL) was treated with CDI (0.653 g) and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (0.668 g) in H₂O (10 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et₂O and washed with 1N HCl (20 mL), sat. NaHCO₃ (20 mL) and water (20 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title compound (0.908 g). Mass spectrum (Cl): 352.
30
35

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Step E 3,4-Dichloro- β -(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide

3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (0.9 g) in CH₂Cl₂ (25 mL) was cooled to -5 to -10°C and treated sequentially with Et₃N (0.332 g), and methanesulfonyl chloride (0.365 g). After two hours the reaction mixture was washed with water(3X20 mL) and the organic layer separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (1.1 g).

10

Step G β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide

3,4-Dichloro- β -(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (1.1 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.14 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted with EtOAc (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH₂Cl₂:MeOH) gave the title compound (0.4 g). M.p. 67-72°, Mass spectrum (FAB): 513 (70%), 511 (100%).

25 Step H 3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide

Oxalyl chloride (7.74 g) in CH₂Cl₂ (80 mL) was added to a -78°C solution of DMSO (9.5 g) in CH₂Cl₂ (30 mL) over 15 mins. This mixture was stirred for 15 minutes whereupon a CH₂Cl₂ (50 mL) solution of 3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (17.15 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with a solution of Et₃N (14.76 g) in CH₂Cl₂ (20 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over MgSO₄,

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filtered and concentrated under reduced pressure to yield an oil (20 g). Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (15.2 g).

5 Step 1 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide
3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (0.43 g), in MeOH (20 mL) was treated sequentially with molecular sieves 3A (2.0 g), 4-phenyl-4-hydroxypiperidine HCl (0.34 g) and
10 NaBH₃CN (0.32 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered through a pad of celite (trademark) and concentrated under reduced pressure. The residue was partitioned between 10% NH₄OH solution and CH₂Cl₂ (25 mL). The organic layer was separated and the aqueous layer
15 extracted with CH₂Cl₂ (2X25 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a crude oil (0.7 g). Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (0.42 g). Mass spectrum (CI): 524.

20

Example 2

1-[3-(3,4-Dichlorophenyl)-5-[(methyl)phenylamino]pentyl]-4-phenyl-4-piperidinol.

25 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide (0.22 g) in THF (25 mL) was treated with BH₃:DMS (0.212 mL; 10 M) and heated at reflux temperature for 18 hours. The cooled reaction mixture was then treated with MeOH (2.0 mL) and the solvent evaporated under reduced pressure. The residue was dissolved in
30 EtOH (20 mL), treated with potassium carbonate (#.# g) and heated at reflux temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and partitioned between CH₂Cl₂ (20 mL) and saturated NaHCO₃ solution (20 mL). The organic portion was separated and the aqueous re-extracted with CH₂Cl₂ (2X20 mL). The combined

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organic was dried over MgSO₄, filtered and evaporated to give the title compound (0.20 g). Mass spectrum (FAB): 515.

Example 3

5 β -(1,3-benzodioxol-5-yl)-4-hydroxy-N-methyl-N,4-diphenyl-1-piperidinepentamide

Step A Diethyl-(1,3-benzodioxol-5-yl)-bis-acetoacetate

Piperonal (25 g) in 95% ethanol (30 mL) was treated with
10 ethylacetoacetate (42.5 mL) and stirred until a homogenous solution was obtained. Piperidine (2.3 mL) was added and the resulting solution stirred 18 hours. The crude product was obtained by filtration and subsequently recrystallized from 95% ethanol to give the title compound (35 g).

15

Step B 3-(1,3-Benzodioxol-5-yl)glutaric acid

Diethyl-3,4-methylenedioxybenzal-bis-acetoacetate (30 g) in ethanol (300 mL) was treated with 50% NaOH (300 mL) and heated at reflux for 4 hours. Approximately 250 mL of solvent removed by distillation. The 20 remaining solution was cooled to 0°C and sufficient HCl was added dropwise to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 x 500 mL) and the combined extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a white solid (19 g).

25

Step C 3-(1,3-Benzodioxol-5-yl)glutaric anhydride

3-(1,3-benzodioxol-5-yl)glutaric acid (3.2 g) was treated with acetyl chloride (15 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene (2 x 100 30 mL) and concentrated under reduced pressure. The residue was slurried with diethyl ether and filtered to afford the title compound (2.91 g).

Step D β -[2-[(phenyl)methylamino]-2-oxoethyl]-1,3-benzodioxol-5-

35 ylpropanoic acid

- 20 -

3-(1,3-Benzodioxol-5-yl)glutaric anhydride (2.91 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with N-methylaniline (1.68 mL), triethylamine (2.16 mL) and DMAP (150 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred 5 for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (300 mL) and washed with 1N HCl (1 x 150 mL) and water (1 x 150 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (4.2 g).

10 **Step E** β (2-hydroxyethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide
 β -[2-[(phenyl)methylamino]-2-oxoethyl]-1,3-benzodioxol-5-yl-propanoic acid (4.2 g) in EtOAc (100 mL) was treated with CDI (2.51 g) and DMAP (146 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.34 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 150 mL), sat. NaHCO₃ (1 x 150 mL) and water (1 x 150 mL).

15 20 The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (2.36 g). Mass spectrum (CI): 328.

25 **Step F** β (2-oxoethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide
A solution of β -(2-hydroxyethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide (500 mg) in CH₂Cl₂ (10 mL) was treated with PDC (570 mg) and molecular sieves (4Å, 570 mg) and stirred at room temperature 30 for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (374 mg).

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Step G β -(1,3-benzodioxol-5-yl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinpentamide

β -(2-oxoethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide (370 mg), in MeOH/THF (1:1, 10 mL) was treated sequentially with

5 molecular sieves 3A (480 mg), 4-phenyl-4-hydroxypiperidine HCl (480 mg) and NaBH₃CN (72 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (10mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 20 mL)

10 The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (310 mg). Mass spectrum (Cl): 487.

15

Example 4

β -(3,4-Difluorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinpentamide

20 Step A Diethyl-3,4-difluorobenzal-bis-acetoacetate
3,4-Difluorobenzaldehyde (5 g) in 95% ethanol (20 mL) was treated with ethylacetoacetate (18 mL) and stirred until a homogenous solution was obtained. Piperidine (1 mL) was added and the resulting solution stirred 18 hours. The crude product was obtained by filtration and

25 subsequently recrystallized from 95% ethanol to give the title compound (11 g).

Step B 3-(3,4-Difluorophenyl)glutaric acid

Diethyl-3,4-difluorobenzal-bis-acetoacetate (11 g) in ethanol (150 mL) was treated with 50% NaOH (150 mL) and heated at reflux for 4 hours. Approximately 100 mL of solvent was removed by distillation. The remaining solution was cooled to 0°C and sufficient HCl was added dropwise to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 x 300 mL) and the combined extracts dried over MgSO₄.

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filtered and concentrated under reduced pressure to give the title compound as a white solid (7.4 g).

Step C 3-(3,4-Difluorophenyl)glutaric anhydride

5 3-(3,4-Difluorophenyl)glutaric acid (7.4 g) was treated with acetyl chloride (50 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene (3 x 100 mL) and concentrated under reduced pressure. The residue was slurried with diethyl ether and filtered to afford the title compound (6.5 g).

10

Step D 3,4-Difluoro- β -[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Difluorophenyl)glutaric anhydride (3.61 g) in CH₂Cl₂ (75 mL) at 0°C was treated sequentially with N-methylaniline (2.16 mL), 15 triethylamine (2.78 mL) and DMAP (195 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (300 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to 20 afford the title compound (4.3 g).

Step E 3,4-Difluoro- β -(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide

3,4-Difluoro- β -[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic 25 acid (4.3 g) in EtOAc (100 mL) was treated with CDI (3.24 g) and DMAP (195 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (3.02 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours.

30 The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 100 mL), sat. NaHCO₃ (1 x 100 mL) and water (1 x 100 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title 35 compound (3.64 g). Mass spectrum (CI): 320.

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Step F_3,4-Difluoro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide

Oxalyl chloride (0.171 mL) in CH₂Cl₂ (10 mL) was added to a -78°C
5 solution of DMSO (0.278 mL) in CH₂Cl₂ over 15 mins. This mixture was
stirred for 15 minutes. Whereupon a CH₂Cl₂ solution of 3,4-difluoro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzene propanamide (500 mg)
was added over 20 minutes. The mixture was stirred for 30 minutes and
then treated with a solution of Et₃N (0.655 mL) in CH₂Cl₂ and stirred for
10 an additional 30 minutes at -78°C, followed by 1.5 hours at room
temperature. The reaction mixture was washed with 0.1 N HCl (1 x 50
mL) and brine (1 x 50 mL). The organic layer was dried over MgSO₄,
filtered and concentrated under reduced pressure to yield an oil. Silica
gel chromatography eluting with 5-15% EtOAc/Hex gave the title
15 compound (388 mg).

Step G_β-(3,4-Difluorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinpentamide

3,4-Difluoro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide (520
20 mg), in MeOH/THF (1:1, 15 mL) was treated sequentially with molecular
sieves 3A (700 mg), 4-phenyl-4-hydroxypiperidine HCl (700 mg) and
NaBH₃CN (103 mg). The resulting mixture was stirred at room
temperature for 18 hours. The reaction mixture was quenched with
water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was
separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL).
The combined organic layers were dried over MgSO₄, filtered and
concentrated under reduced pressure to give the crude oil. Silica gel
chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title
compound (570 mg). Mass spectrum (FAB): 479.2498.

30

Example 5

β-(3,4-Dichlorophenyl)-4-hydroxy-N,4-diphenyl -1-piperidinpentamide

Step A_3,4-Dichloro-β-[(2-phenylamino)-2-oxoethyl]-benzenepropanoic
35 acid

- 24 -

3-(3,4-Dichlorophenyl)glutaric anhydride (5 g, Example 1, Step C) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with aniline (2.19 mL), triethylamine (3.3 mL) and DMAP (236 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred

5 for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (300 mL) and washed with 1N HCl (1 x 150 mL) and water (1 x 150 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (5.4 g).

10 Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-phenylbenzenepropamide 3,4-Dichloro-β-[(2-phenylamino)-2-oxoethyl]-benzenepropanoic acid (4.5 g) in EtOAc (100 mL) was treated with CDI (2.6 g) and DMAP (156 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture

15 was cooled to -10°C and treated with a solution of NaBH₄ (2.42 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 150 mL), sat. NaHCO₃ (1 x 150 mL) and water (1 x 150 mL). The organic phase was dried over MgSO₄, filtered and

20 concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (2 g). Mass spectrum (Cl): 338.

Step C 3,4-Difluoro-β-(2-methanesulfonyloxyethyl)-N-

25 phenylbenzenepropanamide 3,4-Dichloro-β-(2-hydroxyethyl)-N-phenylbenzenepropamide (340 mg) in CH₂Cl₂ was cooled to -5 to -10°C and treated sequentially with Et₃N (0.278 mL) and methanesulfonyl chloride (0.097 mL). After one hour the reaction mixture was diluted with CH₂Cl₂ (75 mL) and washed with sat.

30 NaHCO₃ (1 x 50 mL) The organic layer was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (480 mg).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N,4-diphenyl -1-

35 piperidinepentamide

- 25 -

3,4-Difluoro- β -(2-methanesulfonyloxyethyl)-N-phenylbenzenepropanamide (480 mg) in DMF (5 mL) was treated with 4-phenyl-4-hydroxypiperidine (177 mg) and the mixture stirred at room temperature for 18 hours. The reaction mixture was diluted the EtOAc (50 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc and the combined organic extracts, washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH₂Cl₂:MeOH) gave the title compound (246 mg). Mass spectrum (Cl):

10 497.

Example 6

N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-4-hydroxy-4-phenyl-1-piperidinpentamide

15 Step A 3,4-Dichloro- β -[2-[(4-chlorophenyl)amino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride in CH₂Cl₂ (75 mL) at 0°C was treated sequentially with 4-chloroaniline (2.25 g), triethylamine (1.79 g)
20 and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (3X50 mL) and water (50 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (4.9 g).

25 Step B 3,4-Dichloro- β -(2-hydroxyethyl)-N-(4-chlorophenyl)benzenepropanamide
3,4-Dichloro- β -[2-[(4-chlorophenyl)amino]-2-oxoethyl]benzene propanoic acid (4.0 g) in EtOAc (75 mL) was treated with CDI (2.52 g)
30 and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.59 g) in H₂O (40 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et₂O and
35 washed with 1N HCl (100 mL), sat. NaHCO₃ (100 mL) and water (100

- 26 -

mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title compound (3.81 g).

5 Step C 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-(4-chlorophenyl)benzenepropanamide
3,4-Dichloro-β-(2-hydroxyethyl)-N-(4-chlorophenyl)benzene propanamide (3.5 g) in CH₂Cl₂ (60 mL) was cooled to -5 to -10°C and treated sequentially with Et₃N (1.19 g), and methanesulfonyl chloride (1.35 g). After two hours the reaction mixture was washed with water(3X50 mL) and the organic layer separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (3.8 g).

10 Step D N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-4-hydroxy-4-phenyl-1-piperidine-pentamide
15 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-phenylbenzenepropanamide (3.8 g) in DMF (50 mL) was treated with 4-phenyl-4-hydroxypiperidine (3.74 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (100 mL) and water (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 5% MeOH:CH₂Cl₂ gave the title compound (1.2 g). Mass spectrum (FAB): 386.

Example 7

1-[5-(4-Chlorophenyl)amino]-3-(3,4-dichlorophenyl)pentyl]-4-phenyl-4-piperidinol.

30 The title compound was prepared from N-(4-Chlorophenyl)-β-(3,4-dichlorophenyl)-4-hydroxy-4-phenyl -1-piperidine-pentamide following the procedure of Example 2. Mass spectrum (FAB): 517.

35 Example 8

- 27 -

4-Hydroxy-N-methyl-N-(β , γ -trifluoromethyl-1-piperidinyl)pentanamide

Step A 3-Phenylglutaric anhydride

3-Phenylglutaric acid (100 g) in CH₂Cl₂ (800 mL) was treated with dicyclohexylcarbodiimide (104 g) in CH₂Cl₂ (400 mL) over 30 minutes.

5 The resulting mixture was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with hexane (800 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue crystallized from ethyl acetate/hexane to afford the title compound (53 g).

10

Step B β -[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid
3-Phenylglutaric anhydride (8.0 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with N-methylaniline (5.63 g), triethylamine (5.32 g) and DMAP (1.0 g). The mixture was stirred at 0°C for two hours then

15 allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X50 mL) and water (100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (11.5 g).

20 **Step C β -(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide**
 β -[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (11.5 g) in EtOAc (225 mL) was treated with CDI (11.68 g) and DMAP (1.0 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled

25 to 0°C and treated with a solution of NaBH₄ (9.74 g) in H₂O (150 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et₂O and washed with 1N HCl (100 mL), sat. NaHCO₃ (100 mL) and water (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced

30 pressure to yield the title compound (10.4 g).

Step D β -(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide
 β -(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (5.0 g) in

35 CH₂Cl₂ (100 mL) was cooled to -5 to -10°C and treated sequentially

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with Et₃N (2.23 g), and methanesulfonyl chloride (2.53 g). After two hours the reaction mixture was washed with water(3X50 mL) and the organic layer separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (6.4 g).

5

Step E 4-Hydroxy-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide
β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (2.0 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.44 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (100 mL) and water (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography gave the title compound (0.8 g). Mass spectrum (FAB): 443.

10

15

Example 9

1-[5-[(Phenyl)methylamino]-3-phenylpentyl]-4-phenyl-4-piperidinol.

20

The title compound was prepared from 4-Hydroxy-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide following the procedure of Example 2. Mass spectrum (CI): 429.

25

Example 10

N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-piperidinepentanamide

Step A_β-[2-[(4-chlorophenyl)methylamino]-2-

30

oxoethyl]benzenepropanoic acid

3-Phenylglutaric anhydride (2.0 g) in CH₂Cl₂ (25 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (1.86 g), triethylamine (1.33 g) and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The

35

reaction mixture was washed with 1N HCl (2X50 mL) and water (100

- 29 -

mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (2.7 g).

Step B N-(4-Chlorophenyl)-β-(2-hydroxyethyl)-N-methyl-

5 benzenepropanamide
 β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid
 (1.3 g) in EtOAc (25 mL) was treated with CDI (0.957 g) and DMAP
 (trace). The resulting solution was stirred at room temperature for 15
 minutes and then heated at 50°C for two hours. The reaction mixture
10 was cooled to 0°C and treated with a solution of NaBH₄ (0.983 g) in H₂O
 (15 mL), warmed slowly to room temperature and stirred for 12 hours.
 The reaction mixture was then diluted with Et₂O and washed with 1N
 HCl (20 mL), sat. NaHCO₃ (20 mL) and water (20 mL). The organic
 phase was dried over MgSO₄, filtered and concentrated under reduced
15 pressure to yield the title compound (1.25 g).

Step C N-(4-Chlorophenyl)-β-(2-methanesulfonyloxyethyl)-N-methyl-
benzenepropanamide

N-(4-Chlorophenyl)-β-(2-hydroxyethyl)-N-methyl-benzene propanamide
20 (1.25 g) in CH₂Cl₂ (25 mL) was cooled to -5 to -10°C and treated
 sequentially with Et₃N (0.497 g), and methanesulfonyl chloride (0.563
 g). After two hours the reaction mixture was washed with water(3X25
 mL), sat. NaHCO₃ (20 mL) and the organic layer separated, dried over
 MgSO₄, filtered and concentrated under reduced pressure to give the
25 title compound (1.44 g).

Step D N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-
piperidinepentanamide

N-(4-Chlorophenyl)-β-(2- methanesulfonyloxyethyl)-N-methyl-
30 benzenepropanamide (1.44 g) in DMF (10 mL) was treated with 4-
 phenyl-4-hydroxypiperidine (1.61 g) and the mixture heated at 80°C for
 2 hours. The cooled reaction mixture was diluted the EtOAc (50 mL) and
 water (50 mL) and the aqueous phase removed. The aqueous layer
 was extracted with EtOAc (2X50 mL) and the combined organic extracts,
35 washed with water (50 mL), dried over MgSO₄, filtered and

- 30 -

concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 10% MeOH:CH₂Cl₂ gave the title compound (0.7 g). Mass spectrum (FAB): 477.

5 Example 11

1-[5-[(4-Chlorophenyl)methylamino]-3-phenylpentyl]-4-phenyl-4-piperidinol.

10 The title compound was prepared from N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-piperidinopentanamide following the procedure of Example 2. Mass spectrum (FAB): 463.3.

Example 12

4-(Acetylamino)-N-methyl-N-β,4-triphenyl-1-piperidinopentanamide

15 The title compound was prepared from β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide, (which comes from Example 8, step D), using 4-acetylamino-4-phenylpiperidine hydrochloride in a procedure analogous to that of Example 8, Step E. Mass spectrum
20 (FAB): 484.4.

Example 13

4-(Acetylamino)-N-(4-chlorophenyl)-N-methyl-β,4-diphenyl-1-piperidinopentanamide

25 The title compound was prepared from N-(4-Chlorophenyl)-β-(2-methanesulfonyloxyethyl)-N- methyl- benzene propanamide (which comes from Example 10, Step C), using 4-acetylamino-4-phenylpiperidine hydrochloride in a procedure similar to that of Example
30 10, Step D. Mass spectrum (FAB): 518.3.

Example 14

N-Methyl-N-β-diphenyl-4-(phenylmethyl)-1-piperidinopentanamide

- 31 -

The title compound was prepared from β -(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 8, step D), using a procedure similar to that of Example 8, step E. Mass spectrum (FAB): 441.1.

5

Example 15

N-(4-Chlorophenyl)-N-methyl- β -phenyl-4-(phenylmethyl)-1-piperidinopentanamide

10 The title compound was prepared from N-(4-Chlorophenyl)- β -(2-methanesulfonyloxyethyl)-N- methyl- benzene propanamide (which comes from Example 10, step C), using 4-benzylpiperidine in a procedure similar to that of Example 10, step D. Mass spectrum (FAB): 475.2.

15

Example 16

N-Methyl-N, β -diphenyl-4-(phenylmethyl)-1-piperazinepentanamide

20 The title compound was prepared from β -(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 8, step D), using N-phenylmethylpiperazine in a procedure similar to that of Example 8, Step E. Mass spectrum (FAB): 442.1.

Example 17

25 N-(4-Chlorophenyl)-N-methyl- β -phenyl-4-(phenylmethyl)-1-piperazinepentanamide

30 The title compound was prepared from N-(4-Chlorophenyl)- β -(2-methanesulfonyloxyethyl)-N-methyl-benzene propanamide (which comes from Example 10, step C), using N-phenylmethylpiperazine in a procedure similar to that of Example 10, step D. Mass spectrum (FAB): 476.3.

Example 18

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β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentamide

3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide
5 (which comes from Example 1, step H) (0.53 g), in MeOH (35 mL) was treated sequentially with molecular sieves 3A (5.5 g), isoquinoline HCl (0.33 g) and NaBH₃CN (0.4 g). The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered through a pad of celite (trademark) and concentrated under reduced pressure. The residue was partitioned between 10% NH₄OH solution and CH₂Cl₂ (25 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2X25 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a crude oil (0.7 g). Silica gel chromatography eluting
10 with 2% MeOH/CH₂Cl₂ gave the title compound (0.27 g). Mass spectrum (FAB): 467.
15

Example 19

3-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentanamine
20

The title compound was prepared from β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentamide following the procedure of Example 2. Mass spectrum (FAB): 453.

25

Example 20

β -(3,4-Dichlorophenyl)-3,4-dihydro-6-methoxy-N-methyl-4-oxo-N-phenyl-spiro[2H-1-benzopyran-2,4'-piperidine]-1'-pentamide

30 The title compound was prepared from 3,4-dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 1, Step H) using 3,4-dihydro-6-methoxy-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidine] HCl in a procedure similar to that of Example 18. Mass spectrum (FAB): 581.

35

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Example 21

1'-(3-(3,4-Dichlorophenyl)-5-(methylphenylamino)pentyl]-3,4-dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperid]-4-ol

The title compound was prepared from β -(3,4-Dichlorophenyl)-3,4-dihydro-6-methoxy-N-methyl-4-oxo-N-phenyl-spiro[2H-1-benzopyran-2,4'-piperidine]-1' pentamide following the procedure of Example 2.
Mass spectrum (FAB): 569.

Example 22

10 β -(3,4-Dichlorophenyl)-N-methyl-4-oxo-N-phenyl-1-piperidinepentamide

The title compound was prepared from 3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide (which comes from Example 1 Step H), Mass spectrum (FAB): 433.1457.

15

Example 23

β -(3,4-Dichlorophenyl)-N-methyl-N-phenyl-4-(phenylmethyl)-1-piperidinepentamide

20 The title compound was prepared from 3,4-dichloro- β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 1 Step H), using a procedure similar to that of Example 18. Mass spectrum (FAB): 509.

25 Example 24

N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentanamide

Step A_3,4-Dichloro- β -[2-[(4-chlorophenyl)methylamino]-2-

30 oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (10.0 g) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (6.8 g), triethylamine (4.87 g) and DMAP (0.5 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (3X100 mL)

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and water (100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (14.9 g).

Step B_ 3,4-Dichloro-β-(2-hydroxyethyl)-N-(4-chlorophenyl)-N-

5 methylbenzenepropanamide
3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-
oxoethyl]benzenepropanoic acid (14.9 g) in EtOAc (270 mL) was treated
with CDI (9.1 g) and DMAP (trace). The resulting solution was stirred at
room temperature for 15 minutes and then heated at 50°C for two hours.
10 The reaction mixture was cooled to 0°C and treated with a solution of
NaBH₄ (9.32 g) in H₂O (140 mL), warmed slowly to room temperature
and stirred for 12 hours. The reaction mixture was then diluted with Et₂O
and washed with 1N HCl (3X100 mL), sat. NaHCO₃ (250 mL) and water
(250 mL). The organic phase was dried over MgSO₄, filtered and
15 concentrated under reduced pressure to yield the title compound (12.64
g).

**Step C_ 3,4-Dichloro-β -(2-methanesulfonyloxyethyl)-N-(4-
chlorophenyl)-N-methylbenzenepropanamide**

20 3,4-Dichloro-β -(2-hydroxyethyl)-N-(4-chlorophenyl)-N-
methylbenzenepropanamide (2.1 g) in CH₂Cl₂ (40 mL) was cooled to -5
to -10°C and treated sequentially with Et₃N (0.69 g), and
methanesulfonyl chloride (0.78 g). After two hours the reaction mixture
was washed with water(3X50 mL) and the organic layer separated,
25 dried over MgSO₄, filtered and concentrated under reduced pressure to
give the title compound (2.3 g).

**Step D_N-(4-Chlorophenyl)-β -(3,4-Dichlorophenyl)-4-hydroxy-N-
methyl-4-phenyl-1-piperidinopentanamide**

30 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-
phenylbenzenepropanamide (1.6 g) in DMF (10 mL) was treated with
4-phenyl-4-hydroxypiperidine (0.61 g) and K₂CO₃ (0.476 g). The
mixture was stirred at ambient temperature then diluted with EtOAc (100
mL) and washed with H₂O (2X100 mL). The organic extracts were dried
35 over MgSO₄, filtered and concentrated under reduced pressure to give

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an oil. Silica gel chromatography eluting with 95:5 ($\text{CH}_2\text{Cl}_2:\text{MeOH}$) gave the title compound (0.56 g). Mass spectrum (FAB): 545.3.

Example 25

5 1-[5-(4-Chlorophenyl)(methyl)amino]-3-[3,4-dichlorophenyl]-pentyl-4-phenyl-4-piperidinol.

The title compound was prepared from N-(4-chlorophenyl)- β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentanamide following the procedure of Example 2. Mass spectrum (FAB): 531.1.

Example 26

15 N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-N-methyl-4-oxo-1-piperidinepentanamide

Step A 3,4-Dichloro- β -(2-bromoethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide
3,4-Dichloro- β -(2-methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (6.3 g, from Example 27, Step C) in THF (50 mL) was treated with lithium carbonate (2.0 g) and lithium bromide (2.34 g). The mixture was heated at reflux temperature for 2 hours. The cooled reaction mixture was diluted the CH_2Cl_2 (100 mL) and washed with H_2O (2X100 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to give the title compound as a yellow oil, (5.6 g).

Step B N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-N-methyl-4-oxo-1-piperidine pentanamide
30 3,4-Dichloro- β -(2-bromoethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (4.6 g) in DMF (60 mL) was treated with 4-piperidone monohydrate hydrochloride (3.94 g) and K_2CO_3 (5.3 g). The mixture was stirred vigorously at ambient temperature for 120 hours. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (2X100 mL). The organic extracts were dried over MgSO_4 .

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filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH₂Cl₂:MeOH) gave the title compound (2.25 g). Mass spectrum (FAB): 467.1.

5 Example 27

N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinepentanamide

Step A_3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-

10 oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (2.92 mL), triethylamine (3.36 mL) and DMAP (0.24 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred 15 for 12 hours. The reaction mixture was washed with 1N HCl (2X100 mL) and water (2X100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (6.63 g).

Step B_3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(4-chlorophenyl)-

20 benzenepropanamide

3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]

benzenepropanoic acid (4.0 g) in EtOAc (75 mL) was treated with CDI (2.43 g) and DMAP (0.122 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for one hour. The 25 reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.45 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (100 mL) and washed with H₂O (100 mL), 1N HCl (100 mL), and sat. NaHCO₃ (100 mL). The organic phase was dried over MgSO₄, filtered and 30 concentrated under reduced pressure to yield the title compound (3.69 g).

Step C_3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide

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3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-(4-chlorophenyl)-benzenepropanamide (3.6 g) in CH₂Cl₂ (100 mL) was cooled to -5 to -10°C and treated sequentially with Et₃N (1.62 mL), and methanesulfonyl chloride (0.9 mL). After two hours the reaction mixture 5 was washed with water (100 mL), brine (100 mL) and the organic layer separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (4.3 g).

Step D N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinpentanamide
10 3,4-Dichloro- β -(2-methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (1.6 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.14 g) and K₂CO₃ (0.476 g). The mixture was heated at 60°C for 18 hours. The cooled reaction 15 mixture was diluted the EtOAc (100 mL) and washed with H₂O (2X100 mL). The organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH₂Cl₂:MeOH) gave the title compound (0.56 g). M.p. 67-72°, Mass spectrum (Cl): 543.

20 Example 28

N-(4-Chlorophenyl)-gamma -(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinpentanamine

25 The title compound was prepared from N-(4-Chlorophenyl)- β -(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinpentanamide using the procedure of Example 2. Mass spectrum (Cl): 529.

Example 29

30 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N-(4-methoxyphenyl)-4-phenyl-1-piperidinpentanamide

Step A 3,4-Dichloro- β -[2-[(4-methoxyphenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

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3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with 4-methoxy-N-methylaniline (3.3 g), triethylamine (3.36 mL) and DMAP (0.24 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred 5 for 12 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (7.3 g).

Step B 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-(4-methoxyphenyl)-

10 benzene propanamide
3,4-Dichloro-β-[2-[(4-methoxyphenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (7.2 g) in EtOAc (125 mL) was treated with CDI (4.4 g) and DMAP (0.22 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for one hour.
15 The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (4.46 g) in H₂O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (100 mL) and washed with H₂O (100 mL), 1N HCl (100 mL), and H₂O (100 mL). The organic phase was dried over MgSO₄, filtered and 20 concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 60-100% EtOAc/hexane gave the title compound (5.43 g).

Step C 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-(4-

25 methoxyphenyl)benzene propanamide
3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(4-methoxyphenyl)-benzene propanamide (2.0 g) in CH₂Cl₂ (50 mL) was cooled to -5 to -10°C and treated sequentially with Et₃N (0.911 mL), and 30 methanesulfonyl chloride (0.64 mL). After two hours the reaction mixture was washed with water (100 mL), brine (100 mL) and the organic layer separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (2.56 g).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N-(4-

35 methoxyphenyl)-4-phenyl-1-piperidinopentanamide

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3,4-Dichloro- β -(2-methanesulfonyloxyethyl) -N-methyl-N-(4-methoxyphenyl)benzene propanamide (4.2 g) in DMF (20 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.53g) and K₂CO₃ (1.19 g). The mixture was heated at 60°C for 18 hours. The cooled reaction

5 mixture was diluted the EtOAc (200 mL) and washed with H₂O (3X150 mL). The organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 90:10 (CH₂Cl₂:MeOH) gave the title compound (0.58 g). Mass spectrum (Cl): 541.

10

Example 30

N-[3,5-bis-(Trifluoromethyl)phenyl]- β -(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

15 Step A 3,4-Dichloro- β -[2-[(3,5-bis-trifluoromethylphenyl)amino]-2-oxoethyl]-benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH₂Cl₂ (300 mL) at 0°C was treated sequentially with 3,5-bis-(trifluoromethyl)aniline (7.5 mL), triethylamine (6.7 mL) and DMAP (470 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (18 g).

20

Step B 3,4-Dichloro- β -[2-[(3,5-bis-trifluoromethylphenyl)methylamino]-2-oxoethyl]-benzenepropanoic acid

Sodium hydride (2.16 g, 95%) was suspended in THF (100 mL) and cooled to 0°C. 3,4-Dichloro- β -[2-[(3,5-bis-

30 trifluoromethylphenyl)methylamino]-2-oxoethyl]-benzenepropanoic acid (18 g), in THF (100 mL) was added dropwise. After addition the mixture was warmed to room temperature and stirred for 12 hours. The mixture was then heated at reflux for 1 hour. The mixture was cooled to room temperature and methyl iodide (2.6 mL) was added dropwise. The resulting mixture was heated at reflux for 24 hours. Cooled to 0°C and

35

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quenched carefully with H₂O (100 mL). Extracted with EtOAc (3 x 200 mL). The combine organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give crude product. Silica gel chromatography eluting with 0-50% MeOH/CH₂Cl₂ gave the title
5 compound (8.5 g).

Step C N-(3,5-bis-trifluoromethylphenyl)-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide
3,4-Dichloro-β-[2-[(3,5-bis-trifluoromethylphenyl)methylamino]-2-
10 oxoethyl]-benzenepropanoic acid (7.8 g) in EtOAc (100 mL) was treated with CDI (3.16 g) and DMAP (190 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.95 g) in H₂O (50 mL), warmed slowly to room
15 temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. NaHCO₃ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting
20 with 0-10% MeOH/ CH₂Cl₂ gave the title compound (6 g). Mass spectrum (CI): 488.

Step D N-(3,5-bis-trifluoromethylphenyl)-3,4-dichloro-β-(2-oxoethyl)-N-methyl-benzenepropamide
25 A mixture of N-(3,5-bis-trifluoromethylphenyl)-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide (1.3 g) and molecular sieves (4A, 624 mg) in CH₂Cl₂ (20 mL) and was treated with TPAP (47 mg) and 4-methylmorpholine-N-oxide (624 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad
30 of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (810 mg).

Step E N-[3,5-bis-(Trifluoromethyl)phenyl]-β-(3,4-dichlorophenyl)-4-
35 hydroxy-N-methyl-4-phenyl-1-piperidinpentamide

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N-(3,5-bis-trifluoromethylphenyl)-3,4-dichloro- β -(2-oxoethyl)-N-methylbenzenepropamide (810 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (534 mg), 4-phenyl-4-hydroxypiperidine HCl (534 mg) and NaBH₃CN (104 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (700 mg). Mass spectrum (FAB): 647.1663.

Example 31

15 β -(3,4-dichlorophenyl)-4-hydroxy-N-(2-methoxyphenyl)-N-methyl-4-phenyl-1-piperidinpentamide

Step A 3,4-Dichloro- β -[2-[(2-methoxyphenyl)amino]-2-oxoethyl]-benzenepropanoic acid
20 3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH₂Cl₂ (150 mL) at 0°C was treated sequentially with o-anisidine (6 mL), triethylamine (6.7 mL) and DMAP (440 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (14 g).

Step B 3,4-Dichloro- β -[2-[(2-methoxyphenyl)methylamino]-2-oxoethyl]-benzenepropanoic acid
30 Sodium hydride (1.94 g, 95%) was suspended in THF (100 mL) and cooled to 0°C. 3,4-Dichloro- β -[2-[(2-methoxyphenyl)amino]-2-oxoethyl]-benzenepropanoic acid (14 g), in THF (150 mL) was added dropwise. After addition the mixture was warmed to room temperature and stirred
35 for 12 hours. The mixture was then heated at reflux for 1 hour. The

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mixture was cooled to room temperature and methyl iodide (2.40 mL) was added dropwise. The resulting mixture was heated at reflux for 24 hours. Cooled to 0°C and quenched carefully with H₂O (100 mL). Extracted with EtOAc (3 x 200 mL). The combine organic layers were 5 dried over MgSO₄, filtered and concentrated under reduced pressure to give crude product. Silica gel chromatography eluting with 0-50% MeOH/CH₂Cl₂ gave the title compound (10 g).

Step C 3,4-dichloro-β-(2-hydroxyethyl)-N-(2-methoxyphenyl)-N-
10 methylbenzenepropanamide
3,4-Dichloro-β-[2-[(2-methoxyphenyl)methylamino]-2-oxoethyl]-benzenepropanoic acid (7.8 g) in EtOAc (100 mL) was treated with CDI (3.16 g) and DMAP (190 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The 15 reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.95 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. NaHCO₃ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over MgSO₄, filtered and 20 concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (8 g). Mass spectrum (CI): 382.

Step D 3,4-dichloro-β-N-(2-methoxyphenyl)-N-methyl-(2-oxoethyl)-
25 benzenepropamide
A solution of oxalyl chloride (1.14 mL) in CH₂Cl₂ (50 mL) was cooled to -78°C whereupon DMSO (1.85 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH₂Cl₂ (10 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-(2-methoxyphenyl)-N-
30 methylbenzenepropanamide (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et₃N (7.3 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH₂Cl₂ (100 mL). The organic fraction was separated, 35 washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL)

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and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (950 mg).

- 5 **Step E** β -(3,4-dichlorophenyl)-4-hydroxy-N-(2-methoxyphenyl)-N-methyl-4-phenyl-1-piperidinepentamide
3,4-dichloro- β -N-(2-methoxyphenyl)-N-methyl-(2-oxoethyl)-benzenepropamide (950 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (800 mg), 4-phenyl-4-
- 10 hydroxypiperidine HCl (800 mg) and NaBH₃CN (156 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were
- 15 dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (720 mg). Mass spectrum (CI): 541.
- 20 **Example 32**
1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroquinoline

Step A β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-quinolinepentanoic acid.
3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH₂Cl₂ (300 mL) at 0°C was treated sequentially with 1,2,3,4-tetrahydroquinoline (5.6 mL), triethylamine (6.3 mL) and DMAP (472 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (14.3 g).

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Step B 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroquinoline

β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-quinolinepentanoic acid (14.3 g) in EtOAc (300 mL) was treated with CDI (7.42 g) and DMAP (450 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (5.5 g) in H₂O (100 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (500 mL) and washed with 1N HCl (1 x 200 mL), sat. NaHCO₃ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (11.5 g). Mass spectrum (Cl): 378.

15

Step C 1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroquinoline

A solution of oxalyl chloride (1.15 mL) in CH₂Cl₂ (30 mL) was cooled to -78°C whereupon DMSO (1.87 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH₂Cl₂ (30 mL) solution of 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroquinoline (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et₃N (7.4 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH₂Cl₂ (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (900 mg).

Step E 1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroquinoline
1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroquinoline (900 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with

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molecular sieves 3A (767 mg), 4-phenyl-4-hydroxypiperidine HCl (767 mg) and NaBH₃CN (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was
5 separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (750 mg). Mass spectrum (FAB): 537.2081.

10

Example 33

β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(phenylmethyl)-1-piperidinepentamide

15 Step A 3,4-Dichloro-β-[2-[(phenylmethyl)methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with N-methyl-N-(phenylmethyl)amine (3.0 mL), triethylamine (3.36 mL) and DMAP (0.26)). The mixture was stirred
20 at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (6.9 g).

25 Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide
3,4-Dichloro-β-[2-[(phenylmethyl)methylamino]-2-oxoethyl]benzenepropanoic acid (6.9 g) in EtOAc (150 mL) was treated with CDI (4.4 g) and DMAP (0.22 g). The resulting solution was stirred at
30 room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (4.46 g) in H₂O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL), H₂O (250 mL) and

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dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title compound (6.29 g).

Step C 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide

5 Oxalyl chloride (1.11 mL) in CH₂Cl₂ (10 mL) was added to a -78°C solution of DMSO (1.8 mL) in CH₂Cl₂ (75 mL) over 15 minutes. This mixture was stirred for 15 minutes whereupon a CH₂Cl₂ (20 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide (3.72 g) was added dropwise. The
10 mixture was stirred for 30 minutes and then treated with a solution of Et₃N (4.24 mL) in CH₂Cl₂ (10 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature overnight. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over MgSO₄, filtered and concentrated
15 under reduced pressure to yield an oil (4.3 g). Silica gel chromatography eluting with 1:1/EtOAc:Hex gave the title compound (3.09 g).

Step D β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -N-(phenylmethyl)-1-piperidine pentamide

20 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide (1.21 g), in MeOH (10 mL) was treated sequentially with molecular sieves 3A (0.5 g), 4-phenyl-4-hydroxypiperidine HCl (0.92 g) and NaBH₃CN (0.88 g). The resulting
25 mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. NaHCO₃ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H₂O (50 mL) and CH₂Cl₂ (100 mL). The organic layer was separated and dried over Na₂SO₄, filtered and concentrated under
30 reduced pressure to give the title compound (0.77 g). Mass spectrum (CI): 525.

Example 34

35 1-[3-(3,4-Dichlorophenyl)-5-[methyl(phenylmethyl)amino]pentyl]-4-phenyl-4-piperidinol

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The title compound was prepared from β -(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -N-(phenylmethyl)-1-piperidine pentamide following the procedure of Example 2. Mass spectrum (FAB): 511.4.

5

Example 35

2-[3-(3,4-Dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline

10 Step A β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-isoquinolinepentanoic acid.
3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH₂Cl₂ (300 mL) at 0°C was treated sequentially with 1,2,3,4-tetrahydroisoquinoline (6.0 mL), triethylamine (6.7 mL) and DMAP (472 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (14 g).

15 Step B 2-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline
 β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-isoquinolinepentanoic acid, (14 g) in EtOAc (300 mL) was treated with CDI (7.25 g) and DMAP (440 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (6.7 g) in H₂O (150 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (500 mL) and washed with 1N HCl (1 x 200 mL), sat. NaHCO₃ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (12.4 g). Mass spectrum (CI):

20 378.

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Step C 2-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroisoquinoline

A solution of oxalyl chloride (0.460 mL) in CH₂Cl₂ (20 mL) was cooled to
5 -78°C whereupon DMSO (0.749 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH₂Cl₂ (10 mL) solution of 2-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et₃N (3 mL) and stirred
10 for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH₂Cl₂ (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under
15 reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (800 mg).

Step D 2-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline

20 2-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroisoquinoline (800 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (900 mg), 4-phenyl-4-hydroxypiperidine HCl (900 mg) and NaBH₃CN (130 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction
25 mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2%
30 MeOH/CH₂Cl₂ gave the title compound (810 mg). Mass spectrum (FAB): 537.2075.

Example 36

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-
35 methyl-4-phenyl-1-piperidinepentamide

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Step A 3,4-Dichloro- β -[2-[(3-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (6.7 g) in CH₂Cl₂ (100 mL) at 0°C was treated sequentially with N-methyl-N-[3-methoxyphenyl)methyl]amine (4.7 g), triethylamine (3.27 g) and DMAP (0.32). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (75 mL) and water (2X75 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (10.5 g).

Step B 3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-[3-methoxyphenyl)methyl]benzenepropanamide

3,4-Dichloro- β -[2-[(3-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (10.5 g) in EtOAc (150 mL) was treated with CDI (6.22 g) and DMAP (0.3 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (6.3 g) in H₂O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL), H₂O (250 mL) and dried over MgSO₄, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel chromatography eluting with 5% MeOH/CH₂Cl₂ gave the title compound (9.35 g).

Step C 3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-[3-methoxyphenyl)methyl]benzenepropanamide

Oxalyl chloride (3.23 g) in CH₂Cl₂ (100 mL) was added to a -78°C solution of DMSO (4.14 g) in CH₂Cl₂ (20 mL) over 15 mins. This mixture was stirred for 15 minutes whereupon a CH₂Cl₂ (30 mL) solution of 3,4-Dichloro- β -(2-hydroxyethyl)-N-[3-methoxyphenyl)methyl]benzenepropanamide (8.4 g) was added dropwise. The mixture was stirred for 30 minutes and then treated with a solution of Et₃N (6.43 g) in CH₂Cl₂ (30 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature. The reaction mixture was

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washed with water (100 mL), the organic fraction separated, dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil (11 g). Silica gel chromatography eluting with 10% EtOAc/CH₂Cl₂ gave the title compound (7.75 g).

5

Step D β -(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-[(3-methoxyphenyl)methyl]benzenepropanamide (1.23 g), in MeOH (100 mL) was treated

10 sequentially with molecular sieves 3A (4 g), 4-phenyl-4-hydroxypiperidine HCl (0.87 g) and NaBH₃CN (0.83 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. NaHCO₃ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned

15 between H₂O (50 mL) and CH₂Cl₂ (100 mL). The organic layer was separated and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give an oil (1.8 g). Silica gel chromatography eluting with 5% MeOH/CH₂Cl₂ gave the title compound (0.77 g). Mass spectrum (FAB): 555.

20

Example 37

1-[3-(3,4-Dichlorophenyl)-5-[[3(methoxyphenyl)methyl]methylamino]penty]-4-phenyl-4-piperidinol

25 The title compound was prepared from β -(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide following the procedure of Example 2. Mass spectrum (FAB): 541.

30 Example 38

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]- β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro- β -[2-[[3,5-bis-(trifluoromethyl)phenyl]

35 methyl]methylamino]-2-oxoethyl]-benzenepropanoic acid

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3-(3,4-Dichlorophenyl)glutaric anhydride (3.1 g, Example 1, Step C) in CH₂Cl₂ (50 mL) at 0°C was treated sequentially with 3,5-bis-(trifluoromethyl)benzylamine (3.4 g), triethylamine (1.83 mL) and DMAP (150 mg). The mixture was stirred at 0°C for two hours then allowed to

5 warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (200 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (6.1 g).

10 **Step B** N-[3,5-bis-(trifluoromethyl)phenyl]methyl]-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzene propanamide
3,4-Dichloro-β-[2-[3,5-bis-(trifluoromethyl)phenyl]methyl]methylamino]-2-oxoethyl]-benzenepropanoic acid (6.1 g) in EtOAc (75 mL) was treated with CDI (2.43 g) and DMAP (150 mg). The resulting solution was

15 stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (1.8 g) in H₂O (30 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (150 mL) and washed with 1N HCl (1 x 100 mL), sat.

20 NaHCO₃ (1 x 100 mL) and water (1 x 100 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (5.7 g). Mass spectrum (FAB): 502.0791.

25 **Step C** N-[3,5-bis-(trifluoromethyl)phenyl]methyl]-3,4-dichloro-β-(2-oxoethyl)-N-methyl-benzene propamide
A mixture of N-[3,5-bis-(trifluoromethyl)phenyl]methyl]-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzene propanamide (1.0 g) and molecular

30 sieves (4Å, 460 mg) in CH₂Cl₂ (20 mL) and was treated with TPAP (36 mg) and 4-methylmorpholine-N-oxide (460 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with

35 50-75% EtOAc/Hexanes gave the desired title compound (615 mg).

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Step D N-[{3,5-bis-(trifluoromethyl)phenyl]methyl]-β-(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide
N-(3,5-bis-trifluoromethylphenyl)-3,4-dichloro-β -(2-oxoethyl)-N-methyl-

5 benzenepropamide (615 mg), in MeOH/THF (1:1, 15 mL) was treated sequentially with molecular sieves 3A (525 mg), 4-phenyl-4-hydroxypiperidine HCl (525 mg) and NaBH₃CN (104 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (500 mg). Mass spectrum (FAB): 661.1811.

10

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Example 39

β -(3,4-Dichlorophenyl)-N-[{(3,5-dimethoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide}

20

Step A 3,4-Dichloro-β -[2-{[(3,5-dimethoxyphenyl)methyl]methylamino}-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (6.45 g) in CH₂Cl₂ (60 mL) at 0°C was treated sequentially with N-methyl-N-[3,5-

25

(dimethoxyphenyl)methyl]amine (5.4 g), triethylamine (3.14 g) and DMAP (0.3 g)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the

30

title compound (11.0 g).

Step B 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-[{(3,5-dimethoxyphenyl)methyl]benzenepropanamide

35

3,4-Dichloro-β -[2-{[(3,5-dimethoxyphenyl)methyl]methylamino}-2-oxoethyl]benzenepropanoic acid (11.0 g) in EtOAc (150 mL) was treated

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with CDI (6.08 g) and DMAP (0.3 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (6.2 g) in H₂O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL), H₂O (250 mL) and dried over MgSO₄, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel chromatography eluting with 2.5% MeOH/CH₂Cl₂ gave the title compound (9.1 g).

10

Step C 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide

Oxalyl chloride (3.2 g) in CH₂Cl₂ (125 mL) was cooled to -78°C and treated with a solution of DMSO (4.12 g) in CH₂Cl₂ (20 mL) over 15 minutes. This mixture was stirred for 15 minutes whereupon a CH₂Cl₂ (30 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide (9.0 g) was added dropwise. The mixture was stirred for 30 minutes and then treated with a solution of Et₃N (6.4 g) in CH₂Cl₂ (25 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature. The reaction mixture was washed with water (125 mL), the organic fraction separated, dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil (12 g). Silica gel chromatography eluting with 10% EtOAc/CH₂Cl₂ gave the title compound (8.2 g).

25

Step D β -(3,4-Dichlorophenyl)-N-[(3,5-dimethoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinpentamide

3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide (1.5 g), in MeOH (75 mL) was treated sequentially with molecular sieves 3A (5 g), 4-phenyl-4-hydroxypiperidine HCl (0.98 g) and NaBH₃CN (0.94 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. NaHCO₃ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H₂O (50 mL) and CH₂Cl₂ (100 mL). The organic layer was

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separated and dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give an oil (2.1 g). Silica gel chromatography eluting with 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ gave the title compound (1.2 g). Mass spectrum (FAB): 585.

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Example 40

β -(3,4-Dichlorophenyl)-N-[(3-fluoro-4-methoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

10 Step A 3,4-Dichloro- β -[2-[(3-fluoro-4-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid 3-(3,4-Dichlorophenyl)glutaric anhydride (4.15 g) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with N-methyl-N-[3-fluoro-4-

methoxyphenyl)methyl]amine (3.25 g), triethylamine (2.0 g) and DMAP

15 (0.2)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (75 mL) and water (2X75 mL). The organic layers were dried over MgSO_4 , filtered and concentrated to afford the title compound (7.3 g).

20

Step B 3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-[(3-fluoro-4-methoxyphenyl)methyl]benzenepropanamide

3,4-Dichloro- β -[2-[(3-fluoro-4-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (7.3 g) in EtOAc (150 mL) was treated

25 with CDI (4.15 g) and N,N-dimethylamino pyridine (0.21 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of NaBH_4 (4.2 g) in H_2O (70 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction

30 mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL), H_2O (250 mL) and dried over MgSO_4 , filtered and concentrated under reduced pressure to yield a crude oil (12 g). Silica gel chromatography eluting with 2.5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ gave the title compound (6.35 g).

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Step C 3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-[(3-methoxyphenyl)methyl]benzenepropanamide Oxalyl chloride (1.44 g) in CH₂Cl₂ (100 mL) was cooled to a -78°C and treated with a solution of DMSO (1.84 g) in CH₂Cl₂ (20 mL) over 15 mins. This mixture was stirred 5 for 15 minutes whereupon a CH₂Cl₂ (30 mL) solution of 3,4-Dichloro- β -(2-hydroxyethyl)-N-[(3-fluoro-4-methoxyphenyl)methyl]benzenepropanamide (3.9 g) was added dropwise. The mixture was stirred for 30 minutes, then treated with a solution of Et₃N (2.85 g) in CH₂Cl₂ (20 mL), then stirred for an additional 30 minutes at -78°C, then 10 allowed to warm to ambient temperature. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil (5.0 g). Silica gel chromatography eluting with 10% EtOAc/CH₂Cl₂ gave the title compound (3.6 g).

15 Step D β -(3,4-Dichlorophenyl)-N-[(3-fluoro-4-methoxyphenyl) methyl]-4-hydroxy-N-methyl-1-piperidinpentamide
3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-[(3-fluoro-4-methoxyphenyl)methyl]benzenepropanamide (1.05 g), in MeOH (50 mL) was treated sequentially with molecular sieves 3A (3 g), 4-phenyl-4-hydroxypiperidine HCl (0.71 g) and NaBH₃CN (0.67 g). The resulting 20 mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. NaHCO₃ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H₂O (50 mL) and CH₂Cl₂ (100 mL). The organic layer was separated and dried over MgSO₄, filtered and concentrated under 25 reduced pressure to give an oil (1.2 g). Silica gel chromatography eluting with 5% MeOH/CH₂Cl₂ gave the title compound (0.92 g). Mass spectrum (FAB): 573.

30 Example 41
1-[3-(3,4-Dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1H-indole

Step A 3,4-Dichloro- β -[[2-[1-(indolinyl)]]-2-oxoethyl]-benzenepropanoic acid.

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3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH₂Cl₂ (150 mL) at 0°C was treated sequentially with indole (5.6 g), triethylamine (6.7 mL) and DMAP (440 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred

5 for 12 hours. The reaction mixture was diluted with CH₂Cl₂ (200 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (14 g).

10 **Step B** 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1H-indole 3,4-Dichloro-β-[[2-[1-(indolinyl)]]-2-oxoethyl]-benzenepropanoic acid (14 g) in EtOAc (300 mL) was treated with CDI (12.5 g) and DMAP (470 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled

15 to 0°C and treated with a solution of NaBH₄ (7.3 g) in H₂O (100 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. NaHCO₃ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over MgSO₄, filtered and concentrated

20 under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH₂Cl₂ gave the title compound (5.5 g)

25 **Step C** 1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1H-indole A mixture of 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1H-indole (4.25 g) and molecular sieves (4Å, 2.75 g) in CH₂Cl₂ (40 mL) and was treated with TPAP (50 mg) and 4-methylmorpholine-N-oxide (2.75 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and

30 concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (930 mg).

35 **Step D** 1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1H-indole

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1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1H-indole (740 mg), in MeOH/THF (1:1, 30 mL) was treated sequentially with molecular sieves 3A (880 mg), 4-phenyl-4-hydroxypiperidine HCl (880 mg) and NaBH₃CN (130 mg). The resulting mixture was stirred at room 5 temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel 10 chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (600 mg). Mass spectrum (CI): 521.

Example 42

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-15 methyl-4-phenyl-1-piperidinpentamide

Step A_ 3,4-Dichloro-β-[2-[(2-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (5.9 g) in CH₂Cl₂ (80 mL) at 20 0°C was treated sequentially with N-methyl-N-[2-methoxyphenyl)methyl]amine (3.8 g), triethylamine (3.5 mL) and DMAP (278 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (1 x 100 mL) and brine (1 x 100 mL). The 25 organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (9.3 g).

Step B_ 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide
30 3,4-Dichloro-β-[2-[(2-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (9.3 g) in EtOAc (100 mL) was treated with CDI (4.62 g) and DMAP (345 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a 35 solution of NaBH₄ (3.45 g) in H₂O (50 mL), warmed slowly to room

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temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (1 x 100 mL), H₂O (1 x 100 mL) and dried over MgSO₄, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel

5 chromatography eluting with 5% MeOH/CH₂Cl₂ gave the title compound (8.7 g). Mass spectrum (FAB): 396.1124.

Step C 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide

10 A solution of oxalyl chloride (1.43 mL) in CH₂Cl₂ (30 mL) was cooled to -78°C whereupon DMSO (2.32 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH₂Cl₂ (20 mL) solution of 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide (1.3 g) was added over 20

15 minutes. The mixture was stirred for 30 minutes and then treated with Et₃N (9.2 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH₂Cl₂ (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-100% EtOAc/Hex gave the title compound (950 mg).

20

25 **Step D** β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinpentamide
3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide (950 mg), in MeOH/THF (30 mL, 1:1) was treated sequentially with molecular sieves 3A (770 mg), 4-phenyl-4-

30 hydroxypiperidine HCl (770 mg) and NaBH₃CN (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL) The combined organic layers were

35 dried over MgSO₄, filtered and concentrated under reduced pressure to

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give the crude oil. Silica gel chromatography eluting with 5% MeOH/CH₂Cl₂ gave the title compound (720 mg). Mass spectrum (FAB): 555.2181.

5 **Example 43**

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(2-phenylethyl)-1-piperidinpentamide

Step A 3,4-Dichloro-β-[2-[(2-phenylethyl)methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (3.4 g) in CH₂Cl₂ (50 mL) at 0°C was treated sequentially with N-methylphenethylamine (2.4 mL), triethylamine (2.3 mL) and DMAP (162 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (1 x 100 mL) and brine (1 x 100 mL). The organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (4.6 g).

Step B

3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide
3-3,4-Dichloro-β-[2-[(2-phenethyl)methylamino]-2-oxoethyl]benzenepropanoic acid (4.6 g) in EtOAc (75 mL) was treated with CDI (2.6 g) and DMAP (162 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of NaBH₄ (2.5 g) in H₂O (30 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (1 x 100 mL), H₂O (1 x 100 mL) and dried over MgSO₄, filtered and concentrated under reduced pressure to yield a crude oil (5 g). Silica gel chromatography eluting with 2.5% MeOH/CH₂Cl₂ gave the title compound (3.5 g). Mass spectrum (FAB): 380.1177.

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Step C 3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide

A solution of oxalyl chloride (1.25 mL) in CH₂Cl₂ (25 mL) was cooled to -78°C whereupon DMSO (2.03 mL) was added dropwise over 15 mins.

- 5 This mixture was stirred for 15 minutes. Whereupon a CH₂Cl₂ (25 mL) solution of 3,4-Dichloro- β -(2-hydroxyethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide (1.1 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et₃N (9.2 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at
- 10 room temperature. The reaction mixture was quenched with water and diluted with CH₂Cl₂ (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography
- 15 eluting with 50-100% EtOAc/Hex gave the title compound (900 mg).

Step D β -(3,4-Dichlorophenyl)-4-hydroxy-N-(2-phenethyl)-N-methyl-4-phenyl-1-piperidinepentamide

3,4-Dichloro- β -(2-oxoethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide (900 mg), in MeOH/THF (30 mL, 1:1) was treated sequentially with molecular sieves 3A (800 mg), 4-phenyl-4-hydroxypiperidine HCl (760 mg) and NaBH₃CN (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (20mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH₂Cl₂ gave the title compound (680 mg). Mass spectrum

- 20 (FAB): 539.2222.
- 25
- 30

The *in vitro* and *in vivo* activity of the compounds of formula I can be determined by the following procedures.

In vitro procedure to identify NK₁ activity

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Test compounds are evaluated for their ability to inhibit the activity of the NK₁ agonist Substance P on the isolated guinea pig vas deferens. Freshly cut vas deferens are removed from male Hartley guinea pigs (230-350g) and suspended in 25 ml tissue baths containing

5 Kreb's Henseleit solution warmed to 37°C and constantly aerated with 95% O₂ and 5% CO₂. Tissues are adjusted to 0.5 g and allowed to equilibrate for a period of 30 minutes. The vas deferens are exposed to an electrical field stimulation (Grass S48 Stimulator) every 60 seconds at an intensity that will cause the tissue to contract 80% of its maximum

10 capacity. All responses are recorded isometrically by means of a Grass force displacement transducer (FT03) and Harvard electronic recorder. Substance P inhibits the electrical field stimulated-induced contractions of the guinea pig vas deferens. In unpaired studies, all tissues (control or drug treated) are exposed to cumulative concentrations of Substance

15 P (1×10^{-10} M - 7×10^{-7} M). Single log-concentrations of the test compounds are given to separate tissues and allowed to equilibrate for 30 minutes before a Substance P concentration-response curve is generated. At least 5 separate tissues are used for each control and individual drug-concentration for every drug assay.

20 Inhibition of the Substance P is demonstrated by a rightward shift of its concentration-response curve. These shifts are used to determine the pA₂ value, which is defined as the negative log of the molar concentration of the inhibitor which would require that twice as much agonist be used to elicit a chosen response. This value is used to

25 determine relative antagonist potency.

Isolated Hamster Trachea NK₂ Assay

General methodology and characterization of hamster trachea

30 responses to neurokinin agonists as providing an NK₂ monoreceptor assay is found in C.A. Maggi, et al., *Eur. J. Pharmacol.* 166 (1989) 435 and J.L. Ellis, et al., *J. Pharm. Exp. Ther.* 267 (1993) 95.

Continuous isometric tension monitoring is achieved with Grass FT-03 force displacement transducers connected to Buxco Electronics

35 preamplifiers built into a Graphtec Linearorder Model WR 3310.

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Male Charles River LAK:LVG (SYR) hamsters, 100-200 g fed weight, are stunned by a sharp blow to the head, loss of corneal reflex is assured, the hamsters are sacrificed by thoracotomy and cutting the heart. Cervical trachea segments are removed to room temperature Krebs buffer, pH 7.4, aerated with 95% O₂ - 5% CO₂ gas and cleaned of adhering tissue. The segments are cut into two 3-4 mm long ring segments. Tracheal rings are suspended from transducers and anchored in 15.0 ml water jacketed organ baths by means of stainless steel hooks and 6-0 silk. Baths are filled with Krebs buffer, pH 7.4, maintained at 37°C and continuously aerated with 95% O₂ - 5% CO₂ gas. Tracheal rings are placed under 1.0 g initial tension and allowed a 90 min equilibration period with four 1 µM NKA challenge, wash and recovery cycles at 20 min intervals. 30 min vehicle pretreatment is followed by cumulative additions of rising doses of NKA (3 nM - 1 µM final concentration, 5 min intervals between additions). The final NKA response is followed by a 15 min wash and recovery period. 30 min pretreatment with a test compound or its vehicle is followed by cumulative additions of rising doses of NKA (3 nM - 10 µM final concentration if necessary, 5 min intervals between additions). The final NKA response is followed by a 1 mM carbachol challenge to obtain a maximal tension response in each tissue.

Tissue responses to NKA are recorded as positive pen displacements over baseline and converted to grams tension by comparison to standard weights. Responses are normalized as a % of the maximal tissue tension. ED₅₀'s are calculated for NKA from the control and treated NKA dose responses and compared. Test compounds resulting in an agonist dose ratio ≥ 2 at a screening concentration of 1 µM (i.e. pA₂ ≥ 6.0) are considered actives. Further dose response data is obtained for actives so that an apparent pA₂ estimate can be calculated. pA₂ is calculated either by estimation of K_i as described by Furchtgott (where pA₂ = - Log K_i, R.F. Furchtgott, *Pharm. Rev.* 7 [1995] 183) or by Shild Plot Analysis (O. Arunlakshana & H.O. Shild, *Br. J. Pharmacol.* 14[1959] 48) if the data is sufficient.

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Effect of NK₁ Antagonists on Substance P-Induced Airway Microvascular Leakage In Guinea Pigs

Studies are performed on male Hartley guinea pigs ranging in weight from 400-650 g. The animals are given food and water *ad libitum*. The animals are anesthetized by intraperitoneal injection of dialurethane (containing 0.1 g/ml diallylbarbituric acid, 0.4 g/ml ethylurea and 0.4 g/ml urethane). The trachea is cannulated just below the larynx and the animals are ventilated ($V_T = 4 \text{ ml}$, $f = 45 \text{ breaths/min}$) with a Harvard rodent respirator. The jugular vein is cannulated for the injection of drugs.

The Evans blue dye technique (Danko, G. et al., *Pharmacol. Commun.*, 1, 203-209, 1992) is used to measure airway microvascular leakage (AML). Evans blue (30 mg/kg) is injected intravenously, followed 1 min later by i.v. injection of substance P (10 µg/kg). Five min later, the thorax is opened and a blunt-ended 13-gauge needle passed into the aorta. An incision is made in the right atrium and blood is expelled by flushing 100 ml of saline through the aortic catheter. The lungs and trachea are removed en-bloc and the trachea and bronchi are then blotted dry with filter paper and weighed. Evans blue is extracted by incubation of the tissue at 37°C for 18 hr in 2 ml of formamide in stoppered tubes. The absorbance of the formamide extracts of dye is measured at 620 nm. The amount of dye is calculated by interpolation from a standard curve of Evans blue in the range 0.5-10 µg/ml in formamide. The dye concentration is expressed as ng dye per mg tissue wet weight. Test compounds were suspended in cyclodextran vehicle and given i.v. 5 min before substance P.

Measurement of NK₂ Activity In Vivo

Male Hartley guinea pigs (400-500 gm) with *ad lib.* access to food and water are anesthetized with an intraperitoneal injection of 0.9 ml/kg dialurethane (containing 0.1 g/m diallylbarbituric acid, 0.4 g/ml ethylurea and 0.4 g/ml urethane). After induction of a surgical plane of anesthesia, tracheal, esophageal and jugular venous cannulae are implanted to facilitate mechanical respiration, measurement of esophageal pressure and administration of drugs, respectively.

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The guinea pigs are placed inside a whole body plethysmograph and the catheters connected to outlet ports in the plethysmograph wall. Airflow is measured using a differential pressure transducer (Validyne, Northridge CA, model MP45-1, range $\pm 2 \text{ cmH}_2\text{O}$)

5 which measures the pressure across a wire mesh screen that covers a 1 inch hole in the wall of the plethysmograph. The airflow signal is electrically integrated to a signal proportional to volume.

Transpulmonary pressure is measured as the pressure difference between the trachea and the esophagus using a differential pressure

10 transducer (Validyne, Northridge, CA, model MP45-1, range $\pm 20 \text{ cm H}_2\text{O}$). The volume, airflow and transpulmonary pressure signals are monitored by means of a pulmonary analysis computer (Buxco Electronics, Sharon, CT, model 6) and used for the derivation of pulmonary resistance (R_L) and dynamic lung compliance (C_{Dyn}).

15

Bronchoconstriction Due to NKA

Increasing iv doses of NKA are administered at half log (0.01-3 $\mu\text{g/kg}$) intervals allowing recovery to baseline pulmonary mechanics between each dose. Peak bronchoconstriction occurs within

20 30 seconds after each dose of agonist. The dose response is stopped when C_{Dyn} is reduced 80-90% from baseline. One dose-response to NKA is performed in each animal. Test compounds are suspended in cyclodextran vehicle and given i.v. 5 min before the initiation of the NKA dose response.

25

For each animal, dose response curves to NKA are constructed by plotting the percent increase in R_L or decrease in C_{Dyn} against log dose of agonist. The doses of NKA that increased R_L by 100% (R_L100) or decreased C_{Dyn} by 40% ($C_{Dyn}40$) from baseline values are obtained by log-linear interpolation of the dose response

30 curves.

Neurokinin Receptor Binding Assay(s)

Chinese Hamster ovary (CHO) cells transfected with the coding regions for the human neurokinin 1 (NK₁) of the human

35 neurokinin 2 (NK₂) receptors are grown in Dulbecco's minimal essential

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medium supplemented with 10% fetal calf serum, 0.1 mM non-essential amino acids, 2 mM glutamine, 100 units/ml of penicillin and streptomycin, and 0.8 mg of G418/ml at 37°C in a humidified atmosphere containing 5% CO₂.

5 Cells are detached from T-175 flasks with a sterile solution containing 5 mM EDTA in phosphate buffered saline. Cells are harvested by centrifugation and washed in RPMI media at 40°C for 5 minutes. The pellet is resuspended in Tris-HCl (pH7.4) containing 1 uM phosphoramidon and 4 ug/ml of chymostatin at a cell density of 30 x 10³

10 cells/ml. The suspension is then homogenized in a Brinkman Polytron (setting 5) for 30-45 seconds. The homogenate is centrifuged at 800 x g for 5 min at 4°C to collect unbroken cells and nuclei. The supernatant is centrifuged in a Sorvall RC5C at 19,000 rpm (44,00 x g) for 30 min at 4°C. The pellet is resuspended, an aliquot is removed for a protein

15 determination (BCA) and washed again. The resulting pellet is stored at -80°C.

To assay receptor binding, 50 µl of [³H]-Substance P (9-Sar, 11-Met [02]) (specific activity 41 Ci/mmol) (Dupont-NEN) (0.8 nM for the NK-1 assay) or [³H]-Neurokinin A (specific activity 114 Ci/ mmole) (Zenca) (1.0 nM for the NK-2 assay) is added to tubes containing buffer (50 mM Tris-HCl (pH 7.4) with 1 mM MnCl₂ and 0.2% Bovine Serum Albumin) and either DMSO or test compound. Binding is initiated by the addition of 100µl of membrane (10-20 µg) containing the human NK-1 or NK-2 receptor in a final volume of 200 µl. After 40 minutes at room temperature, the reaction is stopped by rapid filtration onto Whatman GF/C filters which have been presoaked in 0.3% polyethylenimine. Filters are washed 2 times with 3 ml of 50 mM Tris-HCl (pH7.4). Filters are added to 6 mls of Ready-Safe liquid scintillation cocktail and quantified by liquid scintillation spectrometry in a LKB 1219 RackBeta counter. Non-specific binding is determined by the addition of either 1 µM of CP-99994 (NK₁) or 1µM SR-48968 (NK₂) (both synthesized by the chemistry department of Schering-Plough Research Institute). IC₅₀ values are determined from competition binding curves and Ki values are determined according to Cheng and Prusoff using the

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experimentally determined value of 0.8 nM for the NK₁ receptor and 2.4 nM for the NK₂ receptor.

Using the test procedures described above, the following data were obtained for representative compounds of formula I:

5 For all of the compounds of the invention, the NK₁ binding is in a range of about 7-97% inhibition at 1 μ M concentration. For all of the compounds of the invention, the NK₂ binding is in a range of about 0-90% inhibition at 1 μ M concentration. It should be understood that while the NK₂ binding for certain compounds of the invention is as low as 0%
10 at 1 μ M concentration, that at higher concentrations these compounds may have NK₂ binding inhibition activity.

Activities of representative compounds of the invention in the above Neurokinin Receptor Binding Assay are as follows:

15 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl-1-piperidinpentamide

Binding; NK₁ K_i = 150 nM; NK₂ K_i = 5.2 nM.

20 β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(phenylmethyl)-1-piperidinpentamide

Binding; NK₁ K_i = 6.8 nM; NK₂ K_i = 108 nM.

25 β -(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinpentamide
Binding; NK₁ K_i = 12 nM; NK₂ K_i = 215 nM.

30 β -(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinpentamide
Binding; NK₁ K_i = 7.5 nM; NK₂ K_i = 33 nM.

β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(2-phenylethyl)-1-piperidinpentamide
Binding; NK₁ K_i = 70 nM; NK₂ K_i = 46 nM.

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The K_i of a compound is that concentration at which the compound caused 50% inhibition of either NK_1 or NK_2 . For those compounds of the invention having higher than 50% inhibition of NK_1 , K_i 's for NK_1 were determined. The K_i 's for NK_1 for such compounds fell 5 within a range of about 6.8nM to about 215 nM.

For those compounds of the invention having higher than 50% inhibition of NK_2 , K_i 's for NK_2 were determined. The K_i 's for NK_2 for such compounds fell within a range of about 5.2nM to about 215 nM.

It will be recognized that compounds of formula I exhibit NK_1 and 10 NK_2 antagonist activity to varying degrees, i.e., certain compounds have strong NK_1 antagonist activity, but weaker NK_2 antagonist activity. Others are strong NK_2 antagonists, but weaker NK_1 antagonists. While 15 compounds with approximate equipotency are preferred, it is also within the scope of this invention to use compounds of with unequal NK_1/NK_2 antagonist activity when clinically appropriate.

Compounds of formula I have been found to be antagonists of both NK_1 and NK_2 receptors, and are therefore useful in treating conditions caused or aggravated by the activity of NK_1 and NK_2 receptors.

20 The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. Compounds of this invention can be administered in conventional oral dosage forms such as capsules, tablets, powders, cachets, suspensions or solutions, or in injectable 25 dosage forms such as solutions, suspensions, or powders for reconstitution. The pharmaceutical compositions can be prepared with conventional excipients and additives, using well known formulation techniques. Pharmaceutically acceptable excipients and additives include nontoxic and chemically compatible fillers, binders, 30 disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily dose of a compound of formula I for treating asthma, cough, bronchospasm, inflammatory disease, migraine, nociception and gastrointestinal disorders is about 0.1 mg to about 20 35 mg/kg of body weight per day, preferably about 0.5 to about 15 mg/kg,

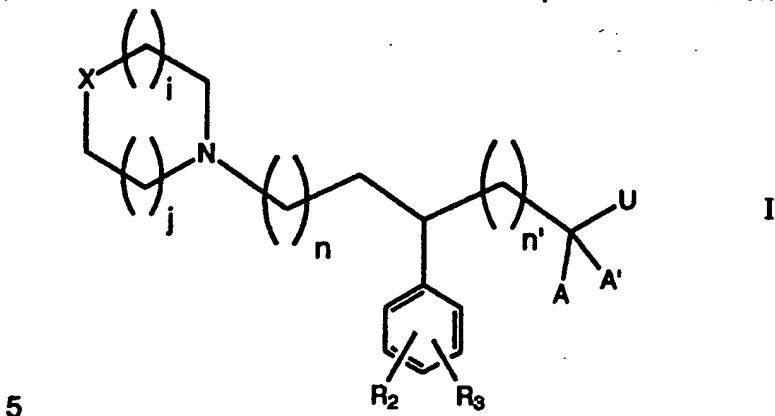
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more preferably 0.5 to about 5 mg/kg. For an average body weight of 70 kg, the dosage range is therefore from about 1 to about 1500 mg of drug per day, preferably about 50 to about 100 mg , given in a single dose or 2-4 divided doses. The exact dose , however is determined by the
5 attending clinician , and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

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WHAT IS CLAIMED IS:

1. The invention relates to compounds of the formula



5

wherein each i and j is independently selected from the group consisting of 1 and 2;

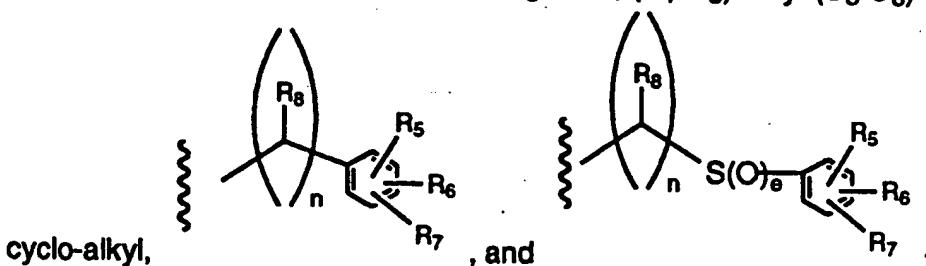
each n is independently selected from the group consisting of 0, 1, 2 and 3; and each n' is independently selected from the group consisting of 1, 2 and 3;

10 wherein A and A' are H, or A and A' taken together are =O, =S; or =N-R₄;

X is selected from the group consisting O, CO, C(R, R₁), C=C(R₁, R₈), NR₁, and S(O)_e wherein e is 0, 1, or 2;

15 R is selected from the group consisting of H, OR₈, CON(R₈)₂, CN, S(O)_eR₈, SO_eN(R₈)₂, CO₂R₈, and NR₄COR₈;

R₁ is selected from the group consisting of H, (C₁-C₆)-alkyl (C₃-C₈)-



20 R₂, R₃, R₅, R₆ and R₇ are independently selected from the group consisting of H, halogen, (C₁-C₆)-alkyl, CF₃, C₂F₅, OR₈, COR₈, CO₂R₈, CON(R₈, R₈), N(R₈, R₈), N(R₈)COR₈, S(O)_eR₈, OC(O)R₄, OC(O)N(R₈, R₄), NR₈CO₂R₄, NR₈(CO)N(R₈, R₈), R₁₅-phenyl, R₁₅-benzyl, NO₂,

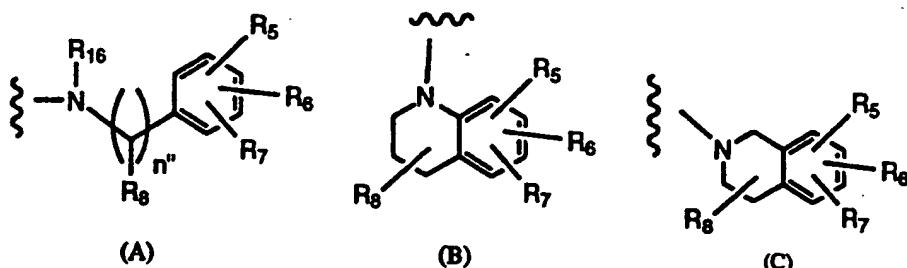
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$\text{NR}_8\text{SO}_2\text{R}_4$, $-\text{S}(\text{O})_2\text{N}(\text{R}_8)_2$ or when R_2 and R_3 or any two of R_5 , R_6 and R_7 are on adjacent carbons they may form a $-\text{O}-\text{CH}_2-\text{O}-$ group:

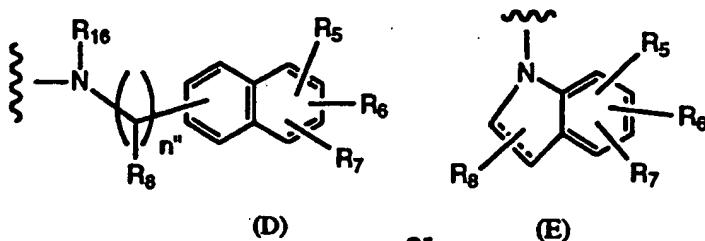
each R₄ is independently selected from the group consisting of alkyl, substituted alkyl, substituted aryl, and substituted benzyl:

5 each R₈ is independently selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, and substituted benzyl;
 each R₁₅ is independently H, halogen, lower alkyl, lower alkoxy; and

U is



10



"n" is independently selected from the group consisting of 0, 1, 2 and 3:

the dashed line is an optional carbon-carbon bond:

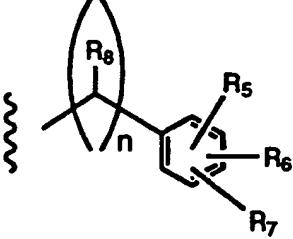
15 R₁₆ is H, (C₁-C₆)-alkyl, -S(O)₂R₄, COR₈, CO₂R₄ where R₄ is not H, CON(R₈)₂. R₁₅-phenyl or R₁₅-benzyl;
substituted means substituted with a substituent selected from the group consisting of H, (C₁-C₆) alkyl, OCF₃, CF₃, and C₂F₅.

20 2. A compound according to claim 1, wherein i is 1 and j is 1.

3. A compound according to claim 1, wherein n is 1, n" is 0, 1, or 2, and n' is 1.

25 4. A compound according to claim 1, wherein n, n', and n" are all 1

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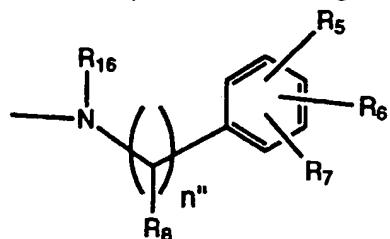
5. A compound according to claim 1, wherein n, and n' are both 1, and n" is 0.
- 5 6. A compound according to claim 1, wherein n, and n' are both 1, and n" is 2.
7. A compound according to claim 1, wherein A and A' are both H
- 10 8. A compound according to claim 1, wherein A and A' taken together are =O.
9. A compound according to claim 1, wherein X is C(R, R₁).
- 15 10. A compound according to claim 1, wherein R is OR₈, CON(R₈)₂ CN, or NR₄COR₄.
11. A compound according to claim 1, wherein X is NR₁.
- 20 12. A compound according to claim 1, wherein R₁ is
13. A compound according to claim 10, where n is 0 or 1 and R₈ is H.
- 25 14. A compound according to claim 10, wherein R₂, R₃, R₅, R₆ and R₇ are H, halogen, C₁-C₆ alkyl, CF₃, OR₈, COR₈, CO₂R₈, CONR₈R₈, or NR₈R₈.
15. A compound according to claim 10, wherein R₁₆ is H or alkyl.

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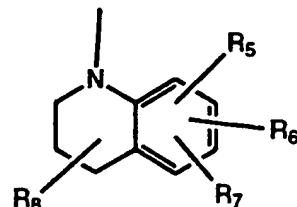
16. A compound according to claim 10, wherein each R₈ is selected from the group consisting of H, C₁-C₆ alkyl, and R₁₅-phenyl.

17. A compound according to claim 10, wherein R₈ is H or substituted alkyl.

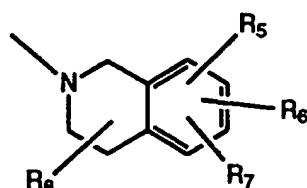
18. A compound according to claim 10, wherein U is



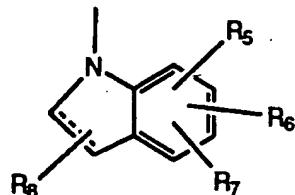
(A)



(B)



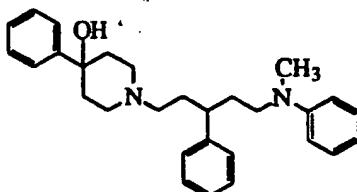
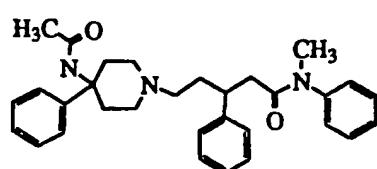
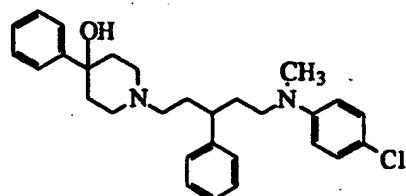
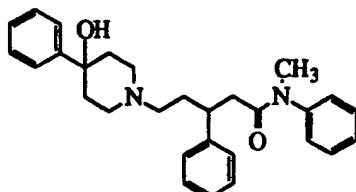
(C)



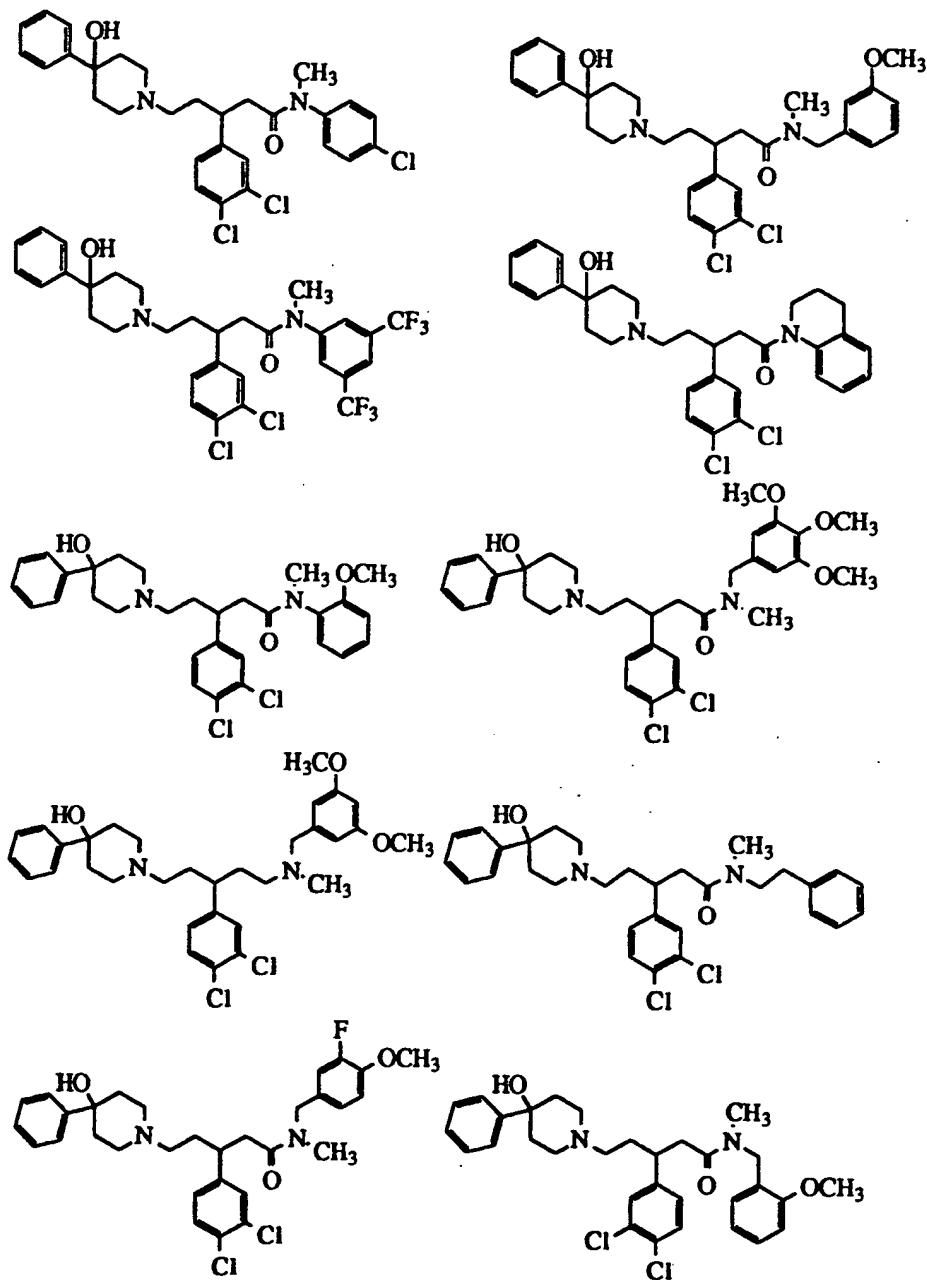
(D)

, or

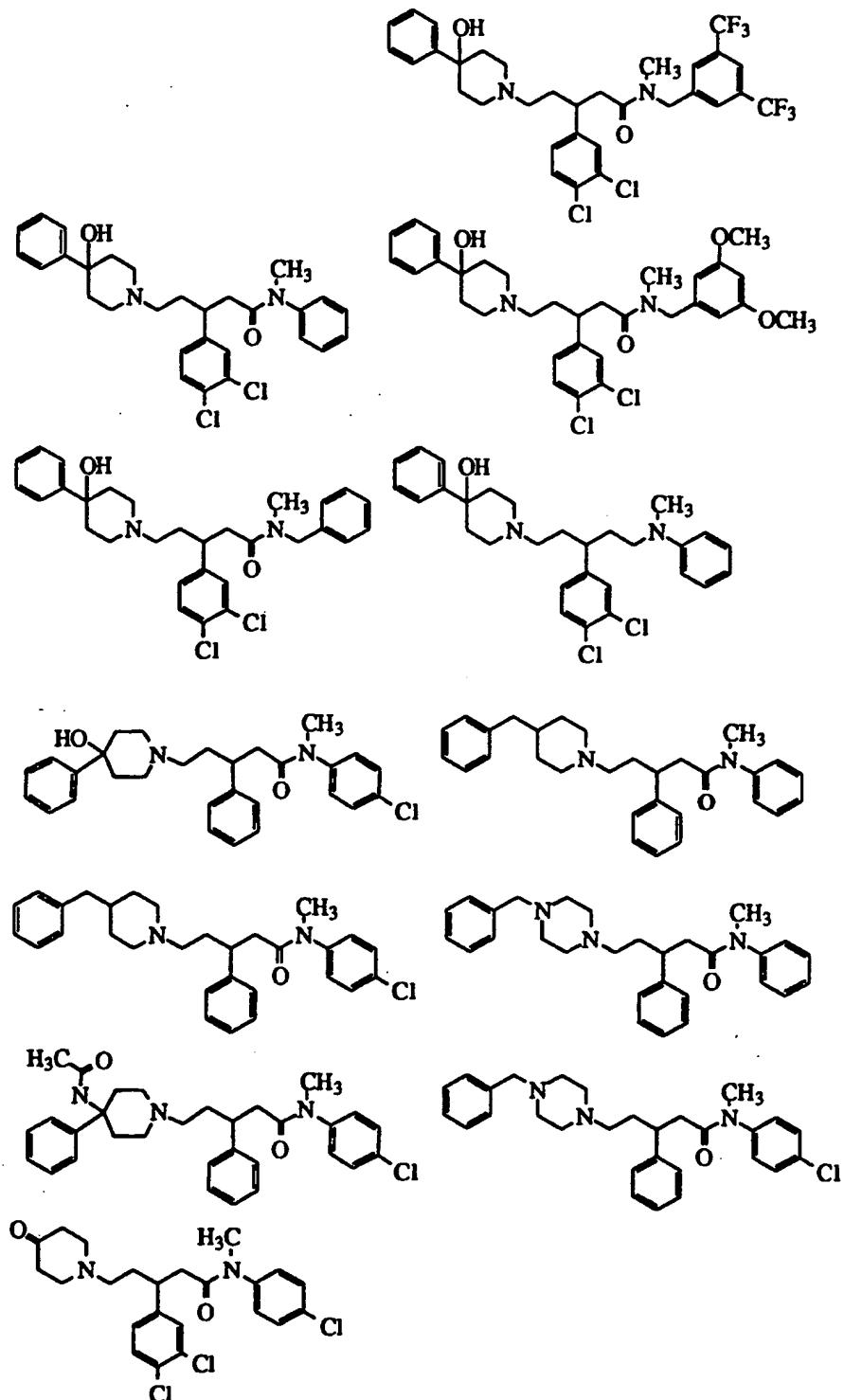
10 19. A compound according to claim 1, selected from the group consisting of



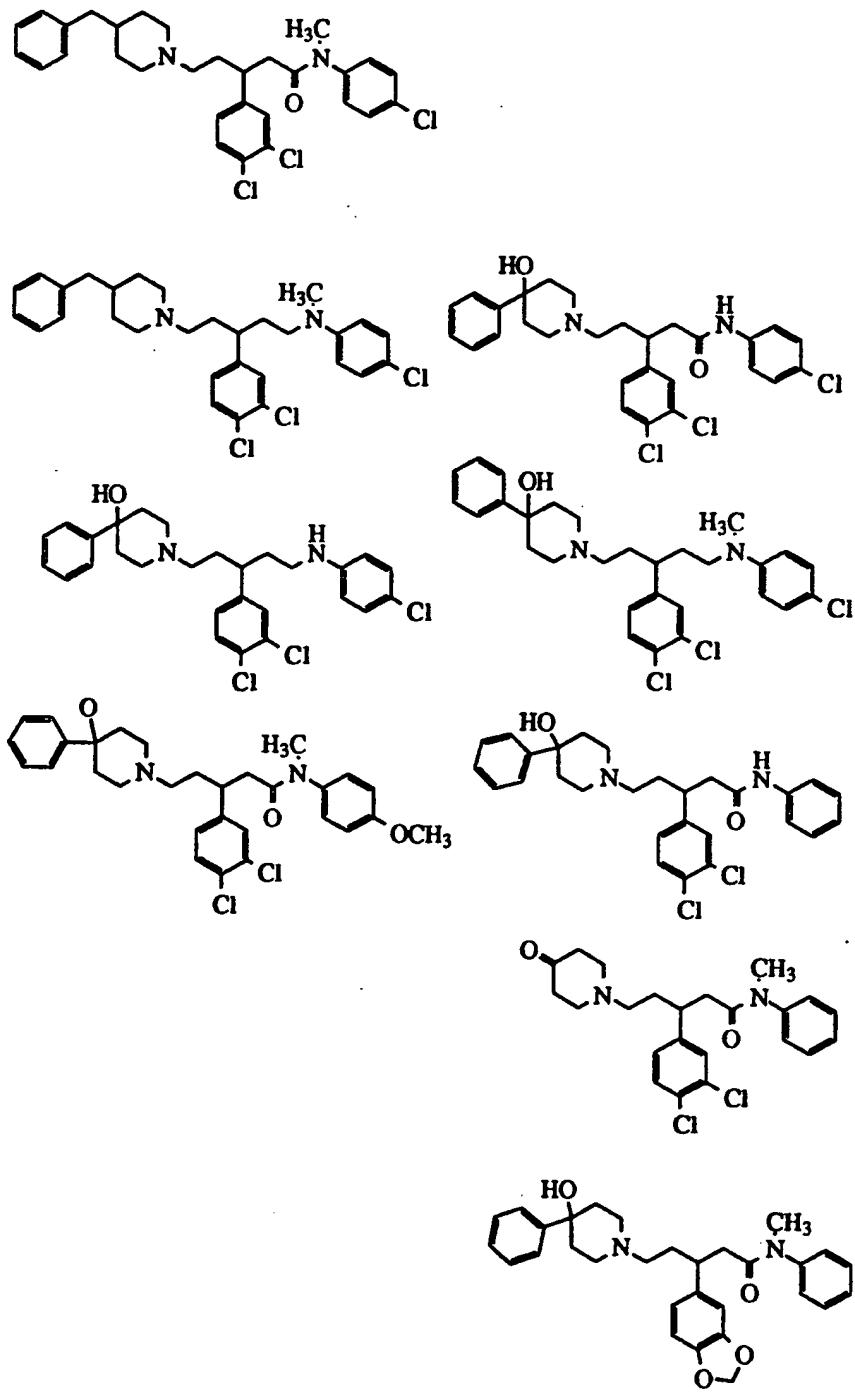
- 73 -



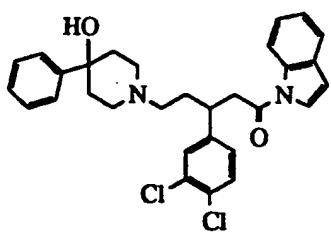
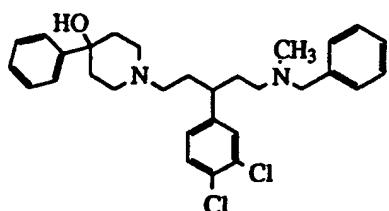
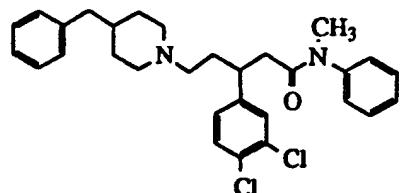
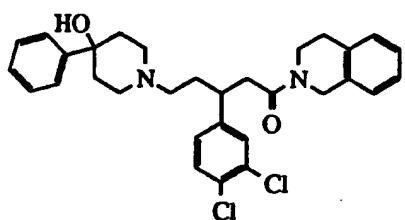
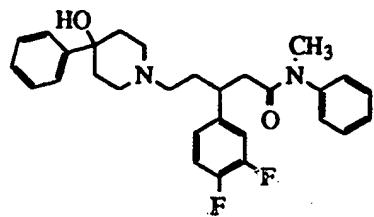
- 74 -

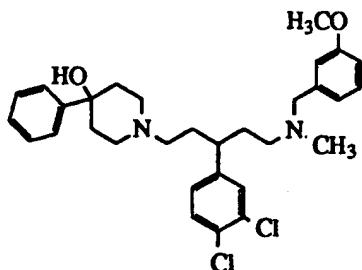


- 75 -



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or a pharmaceutically acceptable salt thereof.

5

20. A composition comprising a neurokinin antagonistic effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier material.

10 21. A method for inducing neurokinin antagonism which comprises administering a neurokinin antagonistic effective amount of a compound according to claim 1 to a mammal in need thereof.

15 22. A method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, osteoarthritis, and rheumatoid arthritis; migraine; central nervous system disorders such as depression, psychosis, dementia, and Alzheimer's disease; Down's syndrome; neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto immune
20 disorders; graft rejection; systemic lupus erythematosus; GI disorders such as Crohn's disease and ulcerative colitis; disorders of bladder function; circulatory disorders such as angina; Raynaud's disease; coughing and pain which comprises administering a neurokinin antagonistic effective amount of a compound according to claim 1 to a
25 mammal in need thereof.

INTERNATIONAL SEARCH REPORT

In _____ Application No
PCT/US 96/07959

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D211/14	C07D211/52	C07D211/58	C07D295/14	C07D211/74
	C07D405/06	C07D401/06	A61K31/445		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 29309 (MERCK AND CO., INC., USA) 22 December 1994 see the whole document ---	1-22
A	WO,A,93 25527 (LUNDBECK, H., A/S, DEN.) 23 December 1993 see abstract ---	1-19
A	GB,A,1 103 524 (INSTITUTO DE ANGELI S.P.A.) 14 February 1968 see the whole document ---	1-22
A	EP,A,0 428 434 (SANOFI SA) 22 May 1991 see the whole document ---	1-22
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
- *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 1996	16.08.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kissler, B

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 96/07959

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO,A,95 26335 (SANOFI SA ;EMONDS ALT XAVIER (FR); PROIETTO VINCENZO (FR); BROECK) 5 October 1995 see the whole document ---	1-22
A	EP,A,0 474 561 (SANOFI SA) 11 March 1992 see the whole document ---	1-22
A	EP,A,0 630 887 (ZENECA LTD) 28 December 1994 see the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/07959

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21 and 22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US96/07959

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Claims 1-18, 20-22 have been searched incompletely.

Obscurity

The generic formula I contains almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

X=N,C, i=j=1, n=n'=1, A and A' are CO, CH₂,

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 96/07959

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CZ-A-	9403122	13-09-95
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		ZA-A-	9304031	07-01-94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 96/07959

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		AU-B-	8354291	12-03-92
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		NO-B-	177226	02-05-95
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		CN-A-	1098094	01-02-95
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